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i. Summary

This thesis presents data relating to the use of hydromorphone for the treatment of acute and chronic pain. The work was done in order to obtain European product licences for both immediate-release and a controlled-release oral formulations.

Hydromorphone is a semi-synthetic derivative of morphine which possesses pharmacologic properties qualitatively similar to those produced by morphine, although it is a more water-soluble molecule and is approximately five-times more potent than morphine. As with all strong opioids, hydromorphone has the potential to produce physical or psychological dependence. Hydromorphone has been credited with a lack of active metabolites in contrast to morphine, which has an active metabolite, morphine-6-glucuronide.

For the immediate-release tablet, hydromorphone is rapidly absorbed after oral administration and undergoes extensive first-pass metabolism, resulting in oral bioavailability of 18.7%. Elimination is multiphasic; there is a rapid decline in plasma concentrations within the first 3 hours after dosing followed by slower elimination phase. The earlier distribution/elimination element is thought to determine hydromorphone's duration of action, whereas the longer elimination half-life of around 15 hours is of less relevance in the clinical setting.

Cmax and AUC(0-24h) for hydromorphone immediate-release are proportional to dose level and there is a statistically significant effect of food, but the effects observed are not clinically relevant. Sex had little effect on the pharmacokinetics of oral immediate-release hydromorphone and age also had little effect. Renal impairment produced changes in the

pharmacokinetics of hydromorphone as did moderate hepatic impairment, both producing an increase in hydromorphone bioavailability.

The controlled-release formulation achieves a very flat profile of release compared with the immediate-release, with Tmax being observed at times in excess of 12 hours. Dose-proportional pharmacokinetics were confirmed and marginally increased bioavailability demonstrated compared with the immediate-release formulation. The effect of food to increase bioavailability is not likely to be clinically significant.

Several published controlled studies of oral hydromorphone in patients with a variety of acute or chronic painful conditions have demonstrated the analgesic efficacy of hydromorphone. Nevertheless, novel studies demonstrating efficacy and safety were requested, therefore, three major studies were conducted to evaluate hydromorphone's efficacy and safety in acute and chronic pain models.

The first of these was a double-blind, single dose, placebo-controlled, multicentre dose-ranging study of 205 postoperative knee replacement patients receiving either 2, 4 or 6 mg single doses of immediate-release hydromorphone. The principal measure of efficacy was the sum of the pain intensity differences (SPID) for pain at rest, using self-reported pain on an 11-point numerical scale over a six-hour period. Hydromorphone 4 and 6 mg were significantly more effective in reducing pain at rest compared with placebo ($p=0.03$ for both comparisons). There was no statistically significant difference between hydromorphone 2mg and placebo. The adjusted means for SPID were -2.3, -5.2, -4.4 and 0.6 for hydromorphone 2, 4 and 6 mg and placebo, respectively. Results were similar for the analyses of SPID for pain on movement. Hydromorphone 4 and 6mg were significantly more effective compared with placebo ($p=0.04$ for both comparisons). There was no

statistically significant difference between hydromorphone 2 mg and placebo (p=0.60). The adjusted means for SPID were –1.3, -5.6, -3.9 and –0.2 for hydromorphone 2, 4 and 6 mg and placebo, respectively. Adverse events were reported by 11 (22%) patients, 15 (31%) patients, 17 (33%) patients and 15 (28%) patients, respectively; and there was no statistically significant difference between the four groups in the proportion of patients who reported adverse events. Nausea, vomiting and pyrexia were the most common adverse events.

The second study was a double-blind, multiple-dose, active-controlled, multicentre, dose-ranging study of 271 postoperative knee replacement patients receiving three-to-six hourly doses of either 2, 4 or 6 mg of immediate-release hydromorphone, compared with 20-mg doses of immediate-release morphine. The principal measure of efficacy was the average pain score (same 11-point scale), calculated using an area-under-the-curve methodology and analysed using equivalence methodology. The adjusted means for the principal measure, namely the AUC (0-48 h) of pain at rest/48 were 4.6 (hydromorphone 2 mg), 4.0 (hydromorphone 4 mg), 3.5 (hydromorphone 6 mg) and 3.9 (morphine sulphate 20 mg). Each dose of hydromorphone was considered equivalent to morphine, based on the 95% confidence intervals falling within the range ± 1.5. Analysis of the AUC (0-48h) of pain on movement/48 for the full analysis set provided adjusted means of 6.6 (hydromorphone 2 mg), 6.1 (hydromorphone 4 mg), 5.7 (hydromorphone 6 mg) and 5.8 (morphine sulphate 20 mg). Adverse events were reported by 42 (62%) patients, 42 (59%) patients, 45 (67%) patients and 38 (58%) patients, respectively; there was no statistically significant difference between the four groups in the proportion of patients who reported adverse events. Nausea, vomiting, pyrexia and sedation were the most common adverse events.

The third study was a double-blind, multiple-dose, active-controlled, multicentre, dose-ranging study of 200 cancer pain patients receiving immediate and controlled-release hydromorphone compared with morphine and analysed using an equivalence methodology. The primary efficacy variable was the patients' self-reported "worst pain" on an 11-point numerical scale. The study showed that there were decreases in worst pain in both treatment groups, confirming the basic efficacy of the two treatments under the study conditions. For the immediate-release formulations, equivalence was proved, again, based on the 95% confidence intervals falling within the range ± 1.5 (mean difference of 0.2, 95% CI –0.4 to 0.9), whereas for the controlled-release formulations, hydromorphone was superior to morphine (mean difference of -0.8, 95% CI –1.6 to –0.01, p=0.046). The overall safety profiles of the two treatments were similar and there were no statistically significant differences between the treatments for the proportion of patients reporting adverse events. The nature of the adverse events reported during hydromorphone and morphine therapy were generally typical of the events associated with these treatments.

This thesis presents three large, multinational positive studies confirming the efficacy and safety of hydromorphone in both acute and chronic pain models.

This thesis is dedicated to my father, John V.G.A Durnin, formerly Professor in the Physiology Department at Glasgow University, who has been nagging me for years to write an MD thesis!

1. Acknowledgement

This work was undertaken by Knoll Pharmaceuticals with the purpose of obtaining product registrations in European states for a range of formulations of hydromorphone. The work was carried out by a large, multinational and multidisciplinary team which included many clinicians working as investigators and consultants. My thanks goes to the many members of this team who made this work possible and enjoyable.

2. Statement of extent of personal contribution

The work presented in this thesis was carried out by Knoll Pharmaceuticals with the aim of achieving product registrations in European states. As such, the contents of this thesis must remain confidential and not be released to third parties without the prior agreement of Abbott Laboratories, (which now owns the proprietary information gathered by Knoll Pharmaceuticals).

The clinical teams involved in this work spanned 8 countries and numbered upwards of 30 individuals. My role, as the Project Clinician, was to design, supervise and report the studies. This involved my collaborating with colleagues and associates for each of the tasks as presented in Table 1.

Table 1. Collaborators in conduct of clinical studies

Discipline	Clinical team leader (Author)	Clinical consultants	Biostatistics	Regulatory Affairs	Clinical Research Associates	Data management	Drug safety	Medical dictionary coding	Medical writers
Task									
Study design	X	X	X	X					
Protocol writing	X	X	X	X	X				
Data collection form design	X	X	X		X	X			
Regulatory approval	X	X	X	X					
Ethics committee approval	X	X	X		X				
Study monitoring	X	X	X		X	X	X		
Data preparation	X	X	X		X	X	X	X	
Data analysis	X	X	X		X				
Report writing	X	X	X		X				X

The tasks listed in Table 1 were team efforts. Nevertheless, as Project Clinician, I held overall responsibility for the project and contributed directly to all of the tasks listed. I was not supported or supervised in these tasks to a substantial degree by any other medical doctor in the employment of Knoll Pharmaceuticals. The clinical experts whom I consulted were medical doctors working in clinical practice and clinical research for various institutions around Europe and North America. This was my major responsibility in the company for a period of approximately four years.

I have included references for all the publications that have been derived from the work presented in this thesis.

The work of preparing this thesis, including review of the literature, has been carried out by me alone, in collaboration with my internal and external thesis advisors as agreed with the Medical Faculty.

3. Introduction

3. Introduction

The under-treatment of pain is still a major public health issue, despite the problem being highlighted in the medical literature. In the postoperative setting, Smith (1998) highlighted a particular deficiency in postoperative pain management. This is what Smith describes as the "gap" between the period immediately after the operation when the patient may be receiving parenteral opioids by a patient-controlled-analgesia (PCA) system and the time when patients are receiving regular oral analgesics such as non-steroidals and simple analgesics. This period was identified by an audit as one requiring research and therapeutic effort to address what was perceived as a time when patients were at an increased risk of poor pain control. Smith identifies oral opioids as the most appropriate treatment for this "gap" period. He describes a specific regimen used at a particular institution comprising twice-daily sustained-release morphine with supplementary doses of immediate-release morphine. However, Smith identifies factors which discourage the use of opioids in the "gap" period. These include the reduction in intensity of the monitoring of patients at this time and the perceived risk from a reduction in gastric emptying in the postoperative period. Specifically, the risk from reduced gastric emptying is the accumulation of opioid in solution within the stomach during the time of stasis and a rapid absorption of the drug load on recommencement of gastric emptying. Smith points out, however, that by using appropriate delays from the time of operation and by observing for clinical signs of the return of gastric emptying, this risk can be greatly reduced.

In the setting of the management of chronic pain caused by cancer, in a study of cancer patients attending clinics in the USA, Cleeland (1994a) established that 42% of those with pain were not given "adequate" analgesic therapy. In this study, 36% of patients reported pain of sufficient severity to interfere with functional ability. Thus, the deficiencies in pain management are an issue of both symptom control and also the consequences of these symptoms. In both this study and a review of a later study (Cleeland 1998), factors predisposing to insufficient pain control were identified. These included older age and minority group status.

These findings in both the postoperative setting and the chronic cancer pain population emerged despite the attempts of various bodies to improve the treatment of patients suffering pain (American Pain Society 1993, Mayor 2000, Phillips 2000, Vastag 2001a,

WHO 1996a, 1996b). Components of the overall phenomenon of the under-treatment of pain are poor recording of pain data in both the postoperative and chronic cancer pain setting (Klopfenstein 2000, Rhodes 2001), insufficient use of a holistic approach to pain treatment (Oliver 2001), lack of knowledge regarding the use of opioids on the part of the medical profession, insufficient variety in types of opioid drugs and formulations in some European countries, difficult administrative barriers to opioid prescribing in some European countries (Mercadante 1998) and misconceptions about opioids (Valera 2000, Zenz 2000). Probably the commonest of the misconceptions on the side of the physician are that opioids are only for use at the end of life and that large proportions of patients receiving opioids will develop psychological dependence. There are a number of concerns being raised in the medical literature at present concerning the risk of the development of psychological dependence to opioids (Passik 2001, Vastag 2001b), but publications suggest that these concerns are not confirmed by the available data (Joranson 2000). Regarding the inadequate recording of pain, the recent Joint Commission on Accreditation of Healthcare Organisations promote the view that pain should be regarded as the "fifth vital sign" in patient care, thus reducing the chance of it being overlooked in the routine management of patients (Phillips 2000).

Many strong opioids are available for the treatment of pain; the "Gold Standard" being morphine. Alternatives are still required, however, because some patients who do not respond well to morphine may respond to alternative opioids (Galer 1992). The studies of what is known as "opioid rotation", or "opioid switching" tend to be retrospective or prospective case series rather than prospective, controlled trials. Nevertheless, there is a strong conviction in the palliative care community that changing an opioid can improve pain control and diminish adverse effects induced by the opioids. Pure opioid agonists such as morphine are known to have no "ceiling effect", in other words, the more of the drug that is administered, the more analgesia will be induced. This means that in practice, the dose of opioid tends to be titrated both against analgesic effect and opioid-induced side effects. In contrast to the pure opioid analgesics, partial opioid agonists such as buprenorphine demonstrate a plateauing of analgesic effect with increasing dose. In the setting of palliative care for cancer pain patients, however, it is predominantly the pure opioid agonists and specifically, morphine, that are advocated. In this setting, the clinical issues encountered are the balance of beneficial analgesic effects from the opioid and the harmful effects of the opioid-induced side effects.

In a retrospective case series published by de Stoutz (1995), 80 patients were treated with opioid rotation for a variety of symptoms experienced on their existing opioid treatment. In these 80 patients, in 53 (66%) cases, the first change in opioid therapy was from morphine to hydromorphone and in 90% of all the changes, only morphine, hydromorphone and methadone were utilised. The dose that the patients were changed to were calculated as being equipotent according to standard conversion tables. In this population, 73% of patients experienced an improvement in symptoms. This would appear to be a positive finding, but it must be remembered that this was conducted with both treating physician and patient being fully aware of what treatments were received and not in the setting of a clinical trial with no controls over other modifications in the patients' overall treatment regimens. De Stoutz postulates that the mechanism of the benefit derived from changing the opioid used is based on the clearance of toxic metabolites from the previous opioid treatment. The lack of good data on the respective metabolite profiles, including pharmacological activity therefrom, make this largely a speculative statement, however.

Given that the gold standard treatment is morphine, it is worth noting that there are conceptual issues based on the very term "morphine" which could have strong connotations in a patient's mind. These beliefs could compromise a patient from receiving ideal treatment for pain control (Kurowska 1996). As such, something as simple as an alternative opioid with a name not associated with morphine could offer advantages to some patients.

In some European states, only controlled-release forms are available for some strong opioids, which necessitates the use of a mixture of opioids in different formulations to provide rescue doses for breakthrough and incident pain. This inevitably compromises clinical care, since there are no data to support the use of a combination of opioids to treat pain (McQuay 1999). This limited availability of strong opioids in a range of formulations, therefore, represents one restriction on practitioners' ability to treat pain optimally. The choice of agents and formulations would be significantly improved if hydromorphone were made available in the three dosage forms described below in all European states.

The deficiencies in current knowledge concerning the "gap" in postoperative pain management and the lack of prospective, blinded comparison of opioids in the treatment of

chronic cancer pain therefore presented an opportunity for study of a range of formulations of an opioid other than morphine in these two indications.

Hydromorphone hydrochloride is a semi-synthetic derivative of morphine. Parenteral formulations and immediate release tablets (Dilaudid IR) have been in clinical use for decades in North America and are indicated for moderate to severe pain, such as that due to surgery, cancer, soft tissue and bone trauma, myocardial infarction, burns and renal colic (Knoll 1997). Immediate-release tablets are usually administered at a starting dose of 2 mg orally every 4 to 6 h as necessary. The dose is currently recommended to be individually adjusted according to the severity of pain, patient response, patient age and weight. Dilaudid CR tablets are a new oral controlled-release form of hydromorphone intended for once-daily administration for the treatment of moderate to severe chronic pain. The Dilaudid CR system allows a relatively constant release of drug over a 24-h period, resulting in stable plasma levels of hydromorphone. Dilaudid CR has been developed in tablets containing 8, 16, 32, or 64 mg hydromorphone.

Knoll Pharmaceuticals embarked on a programme of studies with the aim of registering the new controlled-release form of hydromorphone with the Food and Drug Administration in the USA. At the time that this work was proceeding, a separate programme of studies was begun in Europe with the aim of achieving registration of the existing parenteral formulation and immediate-release tablets as well as the new controlled-release tablets with European regulatory agencies. These agencies requested that these data be collected in an appropriate manner for hydromorphone being regarded as a new chemical entity and not an established and well-characterised molecule. The exception to this was the parenteral formulation, which had existing product licences within the European Union and which could therefore be based on bibliographic data only and not new clinical studies. The requirement, then, was to prove efficacy and safety for both the immediate and the controlled-release tablets.

In the planning process for achieving this aim, it was recognised that there was opinion building within both the medical community treating pain and within the regulatory agencies to the effect that different pain types required separate clinical studies to address efficacy and safety. There are clearly limitations on how many subdivision of pain syndromes could practicably be undertaken in the design of the research programme. The

International Association for the Study of Pain classification of chronic pain alone runs to some 222 pages (IASP 1994). The decision was therefore made to separate chronic pain from acute pain models. This decision was affected, to some degree, by the knowledge of the relatively long time-to-pharmacokinetic-steady-state of the controlled-release formulation and the relatively low expectancy of its utility in acute pain in comparison with the immediate-release formulation.

The acute pain indication appeared to be amenable to a classic approach of a single-dose, placebo-controlled study, followed by a multiple-dose trial. The usual models used for single-dose analgesia trials are postoperative or trauma pain. Since the need was for the trial to explore the use of the immediate-release tablet, the time immediately following that at which the patient ceases to use parenteral opioids by PCA (described as the "gap" above) represented an ideal environment in which to study immediate-release hydromorphone tablets. Knoll Pharmaceuticals had previous experience of studies in postoperative pain which had failed to demonstrate statistical significance compared with placebo. The judgement was that this failure was a result of a lack of homogeneity and insufficient pain stimulus in the pain model used. It was therefore agreed to study only patients recovering from primary knee replacement surgery, a moderate-to-severe pain model. The details of the technical issues around the design of the studies in post-knee replacement are presented in the individual study reports in the main body of the thesis. A major hurdle was encountered at an early stage, however, when concerns were raised by ethics committees regarding the use of placebo in this setting. These concerns were allayed through detailed explanation of the method by which patients received "escape" medication in the placebo-controlled, single-dose study. The whole process of ethical review and the presentation of arguments, which consumed several months, was a reminder of the conflict between the need to collect placebo-controlled data and the need to not compromise patient care (Lyons 1999). The primary efficacy measure seemed self-evident, namely the patient's self-reported pain. However, doubt remained concerning whether the pain in the joint at rest, or on movement should be selected. It was known that mobilisation after surgery is a major issue for knee-replacement patients and it was also self-evident that pain on movement exceeds that at rest. Against this, however, was the expectation that opioids would have more of an effect on pain at rest than on movement (Rainer 2000). Finally, it was decided to select pain at rest as the primary efficacy endpoint and perform the same analysis on pain on movement as a secondary measure. An additional question was which particular pain scale to use. Most

published studies of acute pain over a short period such as six hours used a four-point categorical scale, but the decision was made to use an 11-point numerical scale in order to have a standard score across all of the main efficacy studies in this programme.

The multiple-dose study used the same pain model, but again, because of concerns over the ethics of placebo controls in this setting, an active control (morphine) was selected. The use of morphine as the comparator also met the requirement of the regulatory agencies that the test treatment be compared against the current "gold standard". The knowledge of hydromorphone at the time of designing the comparative study meant that there was a low expectation of being able to demonstrate superiority over morphine in a clinically relevant parameter. The decision was therefore made to design this study on the basis of equivalence. This incurred the problems of requiring a larger study population and also the difficulties in prospectively selecting a "clinically equivalent zone" within which the primary efficacy parameter had to lie. The equivalence zone (or "delta") that was used for the study was $\pm$ 1.5 on the 11-point pain scale from the Brief Pain Inventory. The selection of 1.5 as the value was based on consultation with clinical experts in pain management but it was not possible to validate this with any precise data. The same value has been presented as a clinically significant change on an 11-point scale in published papers and workshops (Rowbotham 1998, Stubhaug 2000). Conversely, various recommendations exist for setting delta, such as half of the difference between active and placebo, 10% of the rating scale or half the standard deviation of the measure at baseline. It is impossible to validate any of these suggestions, however, since they are based on a subjective assessment of what is significant, based on a subjective measure of the pain experienced. One study used data pertaining to the use of breakthrough pain medication, collected in cancer patients, to address this question. The methodology was rather complex and difficult to understand, but the author's suggestion for clinical relevance on an 11-point pain scale was a change of two points (Farrar 2000).

Ideally, an equivalence study should have a sensitivity analysis within its design. This would conventionally be a placebo treatment arm which would allow demonstration of efficacy of the control treatment. This is not ethically feasible within the constraints of a multiple-dose pain study for registration purposes, however. One control which was included in the equivalence methodology is analyses of both a full or "intent to treat" analysis set, as well as a "per protocol" set. The similarity in the results from both these

analyses confirms that the study was conducted with sufficient rigor to prevent an equivalence result simply being the product of regression towards the mean. Finally, the use of three dose levels of the test drug against a single dose level of the comparator in this study raised issues in the equivalence analysis. First, it allowed a form of assay sensitivity, since proof of dose responsiveness would argue against all the treatments lacking efficacy. Second, there was the issue of multiple comparisons within the equivalence methodology. A relatively novel stepped-equivalence methodology was used in order to address this concern (Channon 2000).

The study of chronic pain was determined at an early stage to require cancer pain patients. This was partly because cancer pain is a well-established model for chronic pain, but also because of continuing argument over the appropriateness of long-term opioid treatment for non-malignant chronic pain in Europe (McQuay 2001). As described above, the comparator treatment clearly had to be morphine and since no published study had ever described a statistically significant advantage of one opioid over another in the treatment of chronic pain, and based on our knowledge of hydromorphone, an equivalence methodology was, again, selected.

In both equivalence studies, an interim re-estimation of sample size was incorporated into the design. This had become established practice in Knoll Pharmaceuticals for trials of this kind and had been demonstrated to be acceptable to regulatory authorities, since it did not unblind the data. Additionally, the need for a re-estimation was deemed prudent given that the published data on which the original estimation of sample size was based was not felt to be robust.

The selection of the primary efficacy endpoint for the cancer pain study caused some debate. Given, as described above, that opioids are titrated to effect in respect to pain control and almost equally to adverse effects, it was mooted that the primary comparison in the study should be of adverse effect incidence on the basis of equal pain control in both treatment arms. This was not done, however, since it was deemed counterintuitive to not use a measure of pain as the efficacy variable in an analgesic trial. Additionally, it was not thought to be acceptable to regulatory authorities.

All three clinical trials used a parallel group design. In the acute pain model where patients were recovering from an acute insult, it was not thought appropriate to attempt a crossover design where the baseline pain stimulus would be expected to diminish over the duration of the study. This was thought to be the case in the single-dose study which was of six hours' duration, and more so in the multiple-dose study which was of 48 hours' duration. A crossover design would have been more feasible in the chronic cancer pain population and it would have had the advantage of a reduced patient population for the same power. However, it was recognised that the kinds of cancer pain patients requiring strong opioids are often at the later stage of disease and are therefore less stable. This would have the effect of increasing the dropout rate and invalidating the crossover. Additionally, other events in the management of these patients, such as chemo- or radiotherapy, could interfere with the comparison of one period with another. Also, the need for continuous treatment to manage pain would make it impossible to use washout periods and therefore, carryover effects between the treatment periods could be an issue. Lastly, since the indication sought was the treatment of chronic pain, the treatment durations had to be sufficiently long for the controlled-release therapy to make the comparison clinically valid. Adding to this the need to have the patients titrated to effect on immediate-release treatment prior to switching to controlled-release, the treatment period of weeks would be unwieldy and ethically difficult for a crossover design in this patient population.

In both the postoperative and in the cancer pain setting opioids are rarely used in isolation (Kehlet 1999, Mercadante 2001). However, the trials presented in this thesis were designed as registration studies for European regulatory authorities and as such, they had to focus on the effects of hydromorphone alone. Various items were added to the design and conduct of the studies to try and accommodate this conflict between clinical practice and the need to collect controlled data for registration purposes.

This thesis presents data relating to the use of hydromorphone for the treatment of acute and chronic pain. The data was collected as part of a process to obtain product licences for oral hydromorphone preparations. All of the clinical studies in this thesis were conducted to Good Clinical Practice standards, comprising full Ethics Committee and Regulatory Agency (where appropriate) review and informed consent procedures.

4. Literature data available

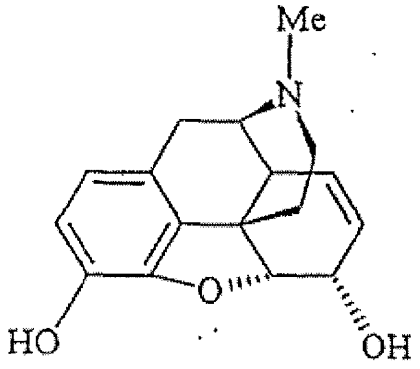
4. Literature data available

4.1 Chemistry

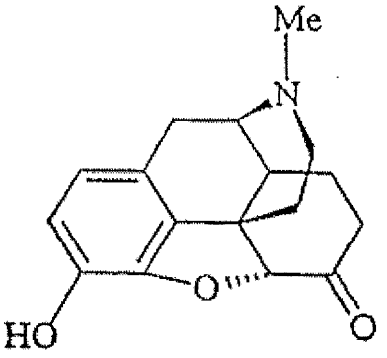
Hydromorphone is a semi-synthetic derivative of morphine; it is commercially available as the hydrochloride salt.

Nomenclature: Hydromorphone hydrochloride 4,5-alpha-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride

Figure 1. structural formula of morphine and hydromorphone (bases):



Morphine



Hydromorphone

Empirical Formula:	$C_{17}H_{19}NO_3HCl$
Appearance:	Fine, white or almost white crystalline powder
Relative Molecular Mass:	321.8
Melting Point:	305 - 315 °C
Solubility:	1 g in ~ 3 ml water; slightly soluble in alcohol

4.2 Pharmacology

4.2.1 Pre-clinical pharmacology

In the scientific literature, nearly all studies carried out with hydromorphone on animals have established the fact that, in general, hydromorphone possesses pharmacologic properties qualitatively similar to those produced by morphine; however, hydromorphone is approximately five times as potent as morphine in various animal models. The fact that hydromorphone is a very potent analgesic *in vivo* is a reflection of its high *in vitro* binding (Chen 1991) since the binding affinity of hydromorphone (K_i = 0.24 nM) to the μ-receptor is 7 times that of morphine (K_i = 1.8 nM) (Mignat 1995). With regard to the binding affinity to other receptor types the selectivity of morphine is 89-fold versus the δ- and 26-fold versus the κ-opioid receptor and that of hydromorphone is 60-fold versus the δ- and 52-fold versus the κ-opioid receptor (Mignat et al 1995). These data show that hydromorphone is directly comparable to the parent compound morphine. Analgesia appeared to correlate with μ-binding affinity (Hennies et al 1988).

The hydromorphone doses given to animals in pharmacology studies were, as a rule, parenterally administered and based on those used in human therapy. However, in many studies higher doses were given, especially if the purpose of the study was to observe non-analgesic effects with a view to gaining insights into possible clinical side effects. The usual test systems were used, i.e. mouse, rat and dog. However, data for other animal species (hamsters, guinea pigs, rabbits, cats, monkeys and sheep) are also available. In all these species, the pharmacologic effects were almost identical in quality.

Hydromorphone produces pronounced antinociception, however, it is evident that the results of the quantitative evaluation of pain threshold depend on the different methods and/or species used (Kraushaar 1953). For example, in *mice* hydromorphone produced a sufficient degree of antinociception after exposure to radiant heat at a subcutaneous ED_{50} of 0.25 mg/kg, whereas in *guinea pigs* the ED_{50} was higher by a factor of 12 (Friebel 1956). Hennies et al (1988) measured the tail flick antinociception against radiant heat in *rats* with intravenous opioid administration and a cut-off time of 12 s. The antinociceptive efficacy was most marked with hydromorphone (ED_{50} 0.28 mg/kg) followed by morphine (ED_{50} 1.37 mg/kg) and other compounds tested. Moreover, the investigators found a fairly good

correlation between the μ-binding affinity and antinociceptive efficacy (correlation coefficient = 0.883; $p < 0.05$). In *rabbits* the antinociceptive effect was determined by means of the tooth-pulp test after intravenous and intraventricular hydromorphone administration (2.5 and 5 mg/kg). The effect peaked in approx. 10 and 120 min, respectively. A comparative study with morphine (5 and 10 mg/kg) revealed a period of 15 and 105 min, respectively (Cube et al 1970).

With regard to the effects on the gastrointestinal system, hydromorphone is, like morphine emetic in the *cat* (0.1 mg/kg IM) and *dog* (0.03 mg/kg S.C.) (Eddy 1934). In addition, hydromorphone increases the tone of the intestine, seen in *rabbits* (0.6 mg/kg S.C.) (Eddy 1934) and *dogs* (0.01 mg/kg) (Walton 1935). Gruber (1935) categorised hydromorphone as about 10 times more effective than morphine, which corresponds approximately to the antinociceptive effect ratio.

Respiratory activity dose-dependently decreased after hydromorphone administration in *dogs, rabbits, guinea pigs* and *rats*. In the *rabbit*, the respiratory rate was lowered to 16% of normal with 2.25 mg/kg IV and the expiratory volume by 50% with 0.2 to 0.3 mg/kg S.C. (Krueger 1943). Overall, hydromorphone proved to be 3 to 9 times more potent than morphine in depressing *rabbit* respiration (Blumberg 1954, King 1935).

The effects on smooth muscles, other than gastrointestinal, are not marked; both tone and activity may be somewhat augmented. Contraction of the vesical sphincter is increased and catheterisation may be necessary (Gruber 1935). The effects on the uterus in situ are a temporary increase in tone and inhibition of the rate and force of contraction in non-pregnant animals, but in pregnant animals these effects are not so marked and diminish greatly as pregnancy advances (Gruber 1935).

With regard to the effects on the central nervous system, excitement or convulsions have been reported in *dogs, cats, rabbits, guinea pigs* and *mice*, but usually with doses considerably larger than those which induce depression (Eddy 1933, Eddy 1934).

With regard to the effects on the eyes, morphine-like drugs induce miosis in *rabbits* (Murray 1982) and *dogs* (Sharpe 1985) as well as mydriasis in *mice* (Rabinowitz 1987), *rats* (Kamenetsky 1997), *cats* (Sharpe 1991) and *monkeys* (Hahnenberger 1980).

According to Hurwitz (1981), hydromorphone, like morphine, had an antidiuretic effect in *mice*; both opioids reduced urine volume to the same extent.

While it has not yet been shown whether hydromorphone has effects on the immune system, a large number of references has dealt with effects of morphine on various immune parameters. Accordingly, morphine is assumed to enhance macrophage apoptosis through accumulation of Bax protein and activation of interleukin converting enzyme 1 (ICE-1) (Singhal 1998) or promote apoptosis via up-regulation of Fas-receptors (Yin 1999).

4.2.2 Clinical pharmacology

4.2.2.1 General

There is extensive available data in the scientific domain with hydromorphone and related opioids and their pharmacology (Reisine 1996). Hydromorphone has qualitative effects similar to those of morphine. The precise mechanism of action of opioid analgesics is not known, but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS). Interaction with the μ-opioid receptor subtype is believed to be responsible for most of hydromorphone's clinical effects. Although estimates vary from study to study, hydromorphone is generally considered to be five to seven times as potent as morphine on a milligram-for-milligram basis. Hydromorphone HCl is also approximately seven times more soluble than morphine in aqueous solution and is therefore capable of being more highly concentrated in parenteral solutions.

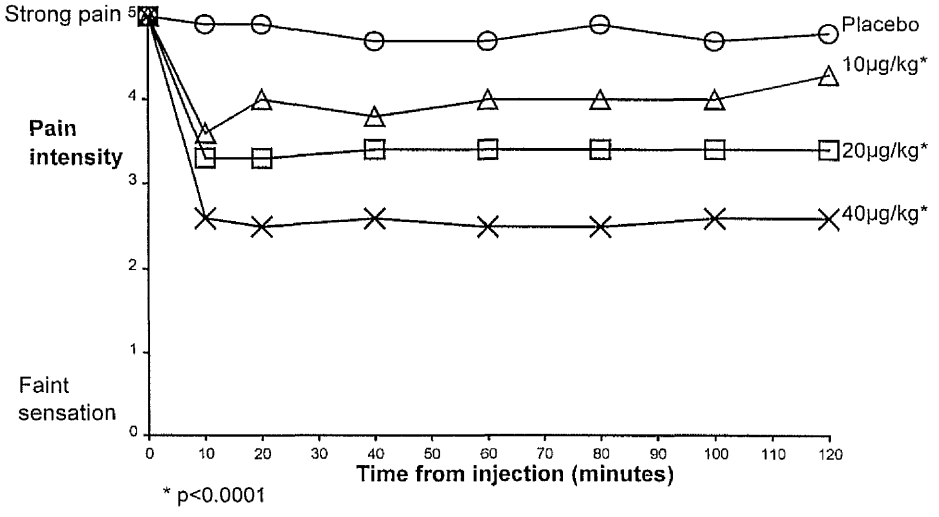
Opioid analgesics, including hydromorphone, exert their primary effects in the CNS and in organs containing smooth muscle, such as the bowel, through interaction with μ-opioid receptors. Neuro-imaging studies have demonstrated the distinction between hydromorphone, as a μ-opioid agonist, compared with a kappa agonist (Schlaepfer 1998). Due to its interaction at the opioid receptors, hydromorphone shares with other opioids the actions, toxicity, and potential for the development of tolerance, physical dependence, and, in susceptible individuals, psychological dependence. As a class, opioids produce dose-related respiratory depression, nausea and vomiting as well as sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, euphoria, anxiety, dysphoria, and other mood changes. Physical responses to the presence of opioids include

miosis, urinary retention, decreased biliary and pancreatic secretions, and increased biliary tract pressure. Constipation occurs frequently and with extended use, opioids may decrease intestinal motility and gastric secretions.

4.2.2.2 Dose responsiveness

In a placebo-controlled, double blind cross-over study, Coda [1997(a)] investigated the analgesic effects of three intravenous bolus doses of hydromorphone (10, 20 and 40 μg/kg) in ten healthy volunteers subjected to the experimental pain model of electrical stimulation of tooth pulp. Significant dose-dependent analgesia was noted ($p<0.001$) (Figure 2) with a rapid onset of action (5 minutes) and maximum analgesic effect between 10 and 20 minutes after maximum plasma hydromorphone concentration had been achieved. However, there was a poor correlation between plasma concentration and effect.

Figure 2. Analgesic effect in experimentally induced pain in 10 healthy volunteers over 2 hours following intravenous bolus injection of different doses of hydromorphone *(Adapted from Coda 1997)*



In a report by Hanna et al (1962), 76 post-operative patients were randomised into a double-blind, crossover study to compare the effects of intra-muscular hydromorphone (1, 2, 3, 4 mg/70 kg) to other opioids [morphine 7, 10 mg / 70 kg, alphaprodine 40 mg / 70 kg, meperidine (pethidine) 75, 100mg / 70 kg]. Patients were observed for three hours after the dose of hydromorphone. In half of the patients, a second drug was used for comparative purposes.

The results shown in Table 2 demonstrated that analgesic effect of hydromorphone was related to the dose received.

Table 2. Analgesic mean scores of hydromorphone (H), morphine (M) and pethidine (P) in post-operative patients at 45, 90, 135 and 180 minutes post dose

Drug	Dose / 70 kg	No of doses	Mean pain relief score				
			45 min	90 min	135 min	180 min	Total
H	1.0	10	1.7	2.2	1.8	1.0	6.7
	2.0	36	1.8	2.5	2.3	2.2	8.8
	3.0	10	1.8	2.7	2.7	2.7	9.9
	4.0	2	1.8	3.0	3.0	3.0	10.8
M	7.0	16	0.9	1.3	1.0	0.5	3.7
	10.0	8	1.9	2.3	2.0	1.7	7.9
P	75.0	17	1.8	2.0	1.4	1.0	6.2
	100.0	9	1.8	1.9	1.8	1.2	6.7

Pain Score: 0=no relief;1=pain less than half gone; 2=pain half gone; 3=complete relief

Mahler and Forrest (1975) reported two double-blind studies in patients with post-operative pain in which each patient received two doses of hydromorphone and two doses of morphine. The doses of hydromorphone used were 0.5 mg, 1 mg and 2 mg, and morphine doses were 5mg and 10mg. Although the statistical analyses were limited in this study, the results demonstrated that intra-muscular hydromorphone was effective in reducing post-operative pain in a dose dependent manner (similar to intra-muscular morphine) as measured by sum of pain intensity differences (SPID) and total pain relief (TOTPAR) (Tables 3 and 4).

Table 3. Weighted mean (SE = pooled standard error) SPID and TOTPAR responses in 52 post-operative patients each of whom received 4 doses of hydromorphone and morphine

Mean (SE) n=52	H 0.5 mg	H 1.0 mg	M 5 mg	M 10 mg
SPID	2.25 (0.27)	3.50 (0.27)	2.39 (0.27)	3.19 (0.27)
TOTPAR	4.27 (0.44)	6.98 (0.44)	5.26 (0.44)	7.00 (0.44)

ANOVAR - for TOTPAR treatment effects ($p<0.005$)

Table 4. Weighted mean (SE = pooled standard error) SPID and TOTPAR responses in 18 post-operative patients each of whom received 4 doses of hydromorphone and morphine

Mean (SE) n=18	H 1 mg	H 2 mg	M 5 mg	M 10 mg
SPID	4.28 (0.57)	5.50 (0.57)	2.57 (0.57)	3.79 (0.57)
TOTPAR	7.33 (0.76)	10.36 (0.76)	4.89 (0.76)	7.74 (0.76)

No statistical analysis

4.2.2.3 Onset of action and duration of effect

4.2.2.3.1 Intramuscular

A plot of the time-effect curves indicated that the average intra-muscular dose of hydromorphone (1.4 mg) has a shorter duration of action than the average intra-muscular dose of morphine (11.3 mg) with a relatively higher peak effect (Houde 1986). The duration of action following intra-muscular administration of equianalgesic intra-muscular doses of hydromorphone and morphine was 4 to 5 hours (Mahler and Forrest, 1975; Houde 1986). The duration of analgesic effect was five hours for hydromorphone 1 mg and morphine 10 mg, and seven hours for hydromorphone 2 mg (Hanna 1962).

In a paper by Brown et al (1973), intra-muscular hydromorphone (0.5, 1 mg) and intra-muscular morphine (5, 10 mg) were compared in a randomised, double blind, crossover study in six volunteers. The time-effect respiratory depression curve for hydromorphone was maximal at the first observation at 30 minutes. The effect was diminishing at the time of the last assessment at 3 hours.

4.2.2.3.2 Intravenous

Following intravenous administration, hydromorphone had a peak effect at 20 min (Seevers 1936). Duration of action following subcutaneous and intravenous administration could not be satisfactorily determined from the study.

4.2.2.3.3 Subcutaneous

Following subcutaneous administration, peak analgesic effect was seen at 90 min with hydromorphone 8 mg (Seevers 1936).

4.2.2.3.4 Oral

Data concerning onset of action of oral hydromorphone is not readily available in the literature, partly, no doubt, because of the technical difficulties in measuring onset of action (Laska 1991). Inferences are often made from pharmacokinetic data, which are presented below and general statements are available as shown in Table 5.

Table 5. Onset and duration of action of oral hydromorphone

Onset of action	Duration of action	Reference	Comments
1.5 to 2 hours	3 to 6 hours	American Pain Society 1990	Slightly shorter duration than morphine
-	4 to 6 hours	Reisine 1996	
0.75 hours*	4 to 6 hours	Knoll Laboratories 1997	
-	2 to 4 hours	Derby 1998	

* by inference from Tmax in pharmacokinetic data

4.2.2.4 Relative potency

4.2.2.4.1 Parenteral administration

The extensive literature review by Eddy et al (1957) concluded that 2.5 mg to 5 mg of hydromorphone can be considered equivalent in analgesic potency to morphine 10 mg (i.e. a relative analgesia potency ratio of 1:2-4). Controlled investigations utilising several

different pain models have indicated that the equianalgesic ratio is somewhat higher- approximately 1:8.

Table 6. Summary of the double-blind studies assessing the relative analgesic potency of hydromorphone and morphine administered intra-muscularly

Reference	n	Model	H:M dose ratio
Goldberg 1965	30	Trauma pain	1:5-7
Hanna 1962	39	Post-operative pain	1:7-10
Mahler 1975	112	Post-operative pain	1:8-10
Seevers 1936	8	Experimental pain	1:10
Houde 1986	48	Cancer pain	1:8

Brown et al (1973) compared the respiratory depressant effects of hydromorphone (0.5, 1 mg) and morphine (5, 10 mg) given intra-muscularly to volunteers. Over the 3-hour observation period, the respiratory depressant relative potency of hydromorphone:morphine was 7.99 (95% CI 5.44 - 10.69) indicating that 1.25 mg of hydromorphone was equivalent to approximately 10 mg of morphine. At peak respiratory depressant effect, the relative potency of H:M was 10.67 (95% CI 2.75 - 87.33) suggesting that approximately 0.95 mg of hydromorphone was equivalent to approximately 10 mg of morphine.

The study of Houde (1986) also investigated the relative analgesic potency of oral to intra-muscular hydromorphone. It was found that the relative potency of oral hydromorphone was 0.2 (or 1/5) of that for the intra-muscular formulation.

4.2.2.4.2 Oral

The values listed in the literature for the equipotency ratio of hydromorphone compared with morphine range from 2 to 10. Table 7 below presents some of the values quoted from different literature sources.

Table 7. Equipotency values for hydromorphone versus morphine

Equipotency value	Comments	Reference
6	Pain relief provided comparable	Knoll Laboratories 1997
8		Reisine 1996
4 to 8*		American Pain Society 1990 (#15)
2.67 to 4*		Derby 1998

* the smaller value is derived from data derived from single-dose studies of morphine

4.2.2.5 Respiratory effects

Respiratory depression was observed in early clinical reports after administration of oral hydromorphone 2 to 2.5 mg (as reviewed by Eddy et al 1957).

The relative potencies of intramuscular hydromorphone and morphine as respiratory depressants have been assayed in healthy volunteers, using a carbon dioxide response curve produced by rebreathing (Brown et al 1973). After randomised, double blind intra-muscular administration of hydromorphone 0.5 and 1 mg and morphine 5 and 10 mg, parallel displacement of the carbon dioxide response curve was consistently observed, with hydromorphone calculated to be eight times as potent as morphine in terms of its respiratory depressant effect. Thus, in this experimental situation, 1.25 mg was equivalent to morphine 10 mg.

Respiratory depression was observed in early clinical reports after administration of subcutaneous hydromorphone 4 to 5 mg (as reviewed by Eddy et al 1957). The respiratory rate fell from 14-17 breaths/minute to 8-9 breaths/minute after administration of hydromorphone 2 mg.

4.2.2.6 Antitussive effects

As reported by Eddy et al (1957), clinical investigation of the antitussive action of hydromorphone was stimulated by work in the rabbit. Most clinical work has been conducted in tuberculosis patients, whose symptoms were typically relieved for 3 to 4 hours after oral hydromorphone 2.5 mg; the antitussive response occurring at a more uniform dosage than the analgesic response. A 2.5-mg dose of hydromorphone was considered to be approximately equipotent to morphine 10 mg, and more effective than codeine 30 mg.

4.2.2.7 Dependence liability

As with all strong opioids, hydromorphone has the potential to produce physical or psychological dependence (addiction) and has been associated with illicit abuse and overdose (Anon, 1988). It should be recognised that physical dependence is not synonymous with psychological dependence (Kanner 1981). In cancer patients receiving long-term treatment, psychological dependence rarely develops. Other surveys of hospital use in medical patients, burns patients and cancer patients also support the view that

medical use of opioids rarely, if ever, leads to drug abuse or iatrogenic psychological dependence (Porter 1980, Perry 1982).

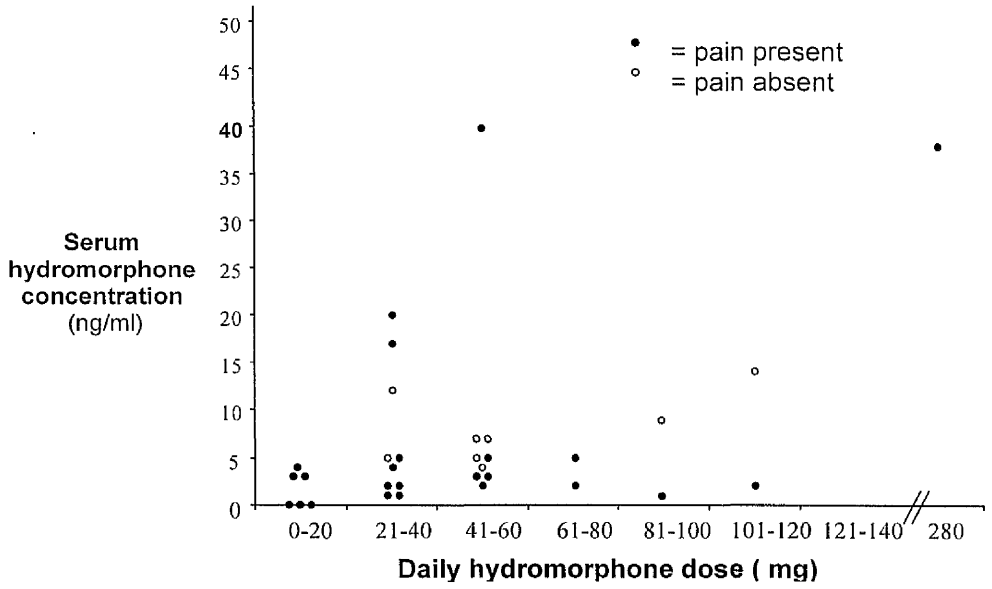
Dependence liability of hydromorphone was discussed by Eddy et al (1957). Euphoria following hydromorphone had been reported in 21/27 published studies between 1926 and 1942. Eddy concluded that hydromorphone had a euphoric action which was "somewhat less" than morphine at "equi-effective" therapeutic doses. He also concluded that it produced a "true addiction" and could effectively sustain morphine addiction at a dose "one-seventh that of morphine". One of the studies referred to by Eddy reported euphoria to be greatest with heroin 2 mg, then morphine 8 mg followed by hydromorphone 1 mg and codeine 64 mg (Seevers 1936).

In a study of the effects of physical dependence, hydromorphone (mean dose 90 mg/day) was substituted for morphine 340 mg/day in seven patients who were psychologically and physically dependent on morphine (Eddy et al 1957). Abrupt drug withdrawal 12 to 17 days after substitution resulted in an abstinence syndrome which developed more rapidly and was more intense but of shorter duration than is typically observed with morphine.

4.2.2.8 Pharmacokinetic / Pharmacodynamic comparisons

Inturrissi (1988) indicated that the degree of pain relief and sedation were a function of plasma concentration for both hydromorphone (n=13) and methadone (n=15) although Reidenberg (1988) found a poor dose-plasma concentration-analgesic effect correlation in a group of 43 patients with chronic severe pain with and without a nerve component (Figure 3). This finding emphasises that inter-patient variability of response to a given dose is not unusual.

Figure 3. Relationship between hydromorphone daily dose, hydromorphone plasma level and pain intensity in 32 patients without nerve pain ***(Adapted from Reidenberg 1988)***



In summary, hydromorphone, like other μ-opioid agonists, has the principal undesirable pharmacological effects of nausea, vomiting, sedation, constipation and respiratory depression. These effects necessitate the use of opioid antagonists when larger doses are studied in healthy volunteers in order to prevent undesirable side effects. They also impair the ability to completely blind a placebo-controlled study of hydromorphone. The unwanted pharmacological effects occur irrespective of the route of administration, but can be minimised by using careful titration and prophylactic treatment as appropriate (Mather 1999).

4.3 Metabolism

4.3.1 Pharmacokinetics and Product Metabolism in Animals

4.3.1.1 Absorption

Absorption of hydromorphone was rapid after oral administration in New Zealand White rabbits (Chang 1988) and after IP administration in rats (Zheng 1997). The plasma pharmacokinetics were very similar across species with linear kinetics, biphasic profiles and rapid disappearance from plasma (Chang 1988). However plasma pharmacokinetics may not reflect pharmacokinetics in the brain (Hartvig 1989). Oral bioavailability in the male rabbit is reported to be 20 % with a plasma half-life of 2.9 hours (Chang 1988). Serum binding is low (19±9%, or less) (Parab 1988, Reidenberg 1988) and is mediated by albumin, with minimal contribution from α_1-acid glycoprotein.

4.3.1.2 Distribution

In the rhesus monkey, opioid receptor binding was greatest in the amygdala (particularly in the anterior portion) followed by the thalamus, hypothalamus, caudate nucleus, and midbrain. Binding was low in the cortex, dentate nucleus of the cerebellum, lower brainstem, and spinal cord (Kuhar 1973). Following intravenous administration of 10-20 μg of radiolabelled hydromorphone to rhesus and cynomolgus monkeys, radioactivity in the brain plateaued at 10-15 min post-injection. In extracranial soft tissue, drug appeared more slowly reaching an uptake of 0.70 at 30 min (Hartvig 1989). Radioactivity in the brain was low in both primate species but the uptake into the brains of rhesus monkeys was 1.4 times that seen in cynomolgus monkeys. Plasma elimination half-lives for the rhesus and cynomolgus monkeys were 50 and 60 min, respectively.

4.3.1.3 Metabolism and excretion

Opioid agonists are metabolised primarily in the liver, with a small amount of metabolic activity also present in the CNS, kidneys, lungs, and placenta (AHFS 1996). In the rabbit, hydromorphone is metabolised by conjugation and reduction to form the 6-α- and 6-β-OH metabolites, dihydromorphine and dihydroisomorphine (Cone 1977). Hydromorphone is eliminated in a biphasic manner - elimination rate constants after IV (5 mg/kg) and oral (20 mg/kg) administration in the rabbit were ~ 0.29 and ~ 0.24, respectively (Chang 1988).

After a single-dose of hydromorphone, the parent compound and both the 6-α- and 6-β-OH metabolites were present in the urine of rats, guinea pigs, rabbits, dogs and humans (Cone 1977). Free or conjugated hydromorphone predominated: levels of free or conjugated 6-β-OH metabolites were generally equal to or higher than those of the 6-α-OH metabolites. Levels of these two metabolites were higher in the guinea pig than in the other species studied (8 % and 20 % for the α- and β- forms, respectively, in the guinea pig, 1 - 2 % and 2 - 5 % respectively in other species). Total recovery of drug and metabolite from the urine of the rat, guinea pig, rabbit and dog were 32 %, 73 %, 28.6 % and 65.4 %, respectively. The time course for excretion of drug was similar between species with a large majority of drug being excreted within 24 h.

4.3.2 Metabolism and Pharmacokinetics in man

4.3.2.1 Metabolism

Hydromorphone has been credited with a lack of active metabolites in contrast to morphine, which has an active metabolite, morphine-6-glucuronide (Mather 1999). Indeed, this active metabolite is being investigated as an analgesia development project by the pharmaceutical company, CeNeS (Anon. 2001). The site of production of the glucuronides to morphine and hydromorphone is assumed to be the liver, although for morphine, there is evidence that considerable glucuronidation takes place in the intestine (Mikus 1999).

In a study of 24 cancer pain patients receiving variable doses of hydromorphone by the oral or subcutaneous route, single blood samples were used to examine metabolite profiles (Quigley 1999). The principal metabolite was hydromorphone-3-glucuronide, with a 61:1 ratio for H-3-G:HM. Other metabolites identified were dihydromorphine-6-glucuronide (ratio 1.7:1) and dihydromorphine (ratio 0.5:1). The authors suggest that the 6-glucuronide metabolite may have pharmacological activity. The authors do not comment on different ratios when parenteral and oral routes were compared – with hydromorphone being subject to significant first-pass metabolism, this factor would be expected to be important. In a further study of 18 patients with chronic cancer pain, Hagen (1995) reported a 27:1 ratio of H-3-G to parent.

Urinary excretion of hydromorphone is predominantly in the form of the glucuronide (37.9% of administered dose), with 5.6% being free hydromorphone. Of the conjugated drug, 1.1% of the administered dose was hydroxy metabolites (Cone 1977).

No references relating to hydromorphone interactions were found in the literature, and examples for morphine do not give a consistent indication of known interactions.

4.3.2.2 Pharmacokinetics

4.3.2.2.1 General

Hydromorphone is rapidly absorbed after oral administration and undergoes extensive first-pass metabolism, resulting in oral bioavailability of 18.7% (Drover 1999) not disimilar to morphine (29.2%, Hasselstrom 1993). The bioavailability for rectal administration is reported as 33% (Parab 1988), but this same paper quotes a value of 50.7% for oral bioavailability. The inflated value for oral bioavailability may be a reflection of a less specific assay (Hind 2000) in this study. This would, therefore, suggest that in reality, bioavailability via the rectal route is well below the 33% value quoted. Hydromorphone crosses the placenta (Martindale 1993) and is found in low levels in breast milk (Ellenhorn 1988). Serum protein binding (species not specified) is quoted as 7.1% and the volume of distribution is 2.9 L/kg (Parab 1988).

4.3.2.2.2 Intravenous administration

Parab (1988) reports that after administration of a 2-mg intravenous dose of hydromorphone to a group of nine healthy male volunteers, three minutes after administration of the dose, 63% of the administered hydromorphone had left the plasma and distributed to other tissues. The authors reported that this was consistent with findings from studies in mice where hydromorphone had distributed within 3.5 minutes of rapid intravenous infusion to well perfused organs such as the liver, spleen, kidney and skeletal muscle. The plasma concentration-time curve showed a distinct distribution phase followed by a terminal elimination phase. Parab quotes a distribution half-life of 0.07 hours. A terminal elimination half-life of 2.36 hours is quoted, but these data are based on a less specific assay method than that used in the current set of studies described below (Hind 2000). Hill (1991) confirmed that pharmacokinetics of 45-second intravenous infusions were dose-proportional over the dose range 10 to 40 μg/kg.

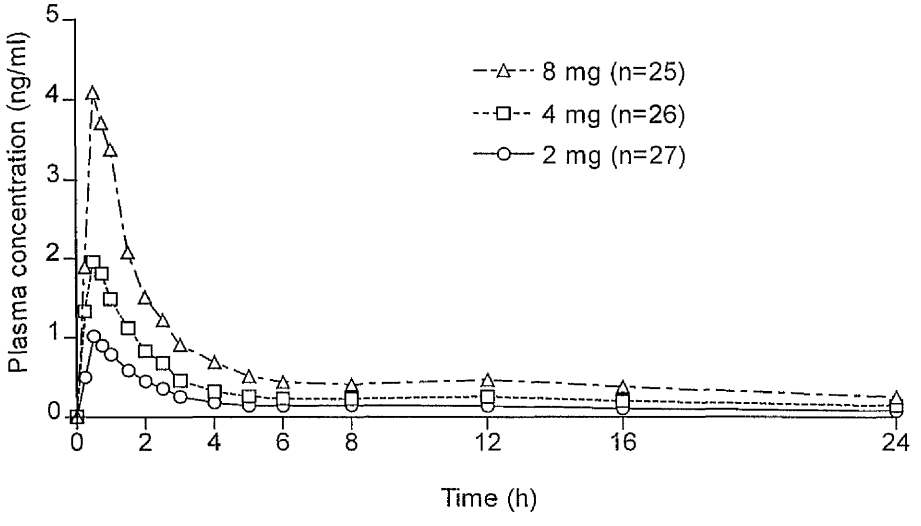
4.3.2.2.3 Immediate-release formulation

4.3.2.2.3.1 PHARMACOKINETICS AND DOSE PROPORTIONALITY

In an open, randomised, three-way crossover study in 27 healthy male Caucasian volunteers, aged from 19 to 53 years, the dose proportionality and the pharmacokinetics of immediate-release hydromorphone following single oral doses of 2 mg, 4 mg and 8 mg were examined (Durnin 2001a). The statistical testing performed consisted of 90% confidence intervals (CIs) based on the differences between doses (pairwise comparisons) as a test of dose proportionality where Cmax and AUC were dose adjusted and log-transformed prior to analysis. Also, a regression analysis of Cmax and AUC with dose was used to examine linearity across all dose levels simultaneously, as a test of dose proportionality.

Hydromorphone was rapidly absorbed into the systemic circulation, reaching peak plasma concentrations within 1 hour of dosing (Figure 4). Elimination was multiphasic; there was a rapid decline in plasma concentrations within the first 3 hours after dosing followed by slower elimination. Because of the secondary peaking, kel was poorly defined for many of the profiles and hence AUC(0-∞) was unavailable for use in the analysis of dose proportionality.

Figure 4. Mean plasma concentrations of hydromorphone following single oral doses of hydromorphone IR to healthy volunteers



The statistical regression analysis indicated that Cmax and AUC(0-24h) for hydromorphone were proportional to dose level (Table 8). With a doubling of dose, increases of 104% and 88% were estimated for these parameters, respectively.

Table 8. Mean pharmacokinetic parameters of hydromorphone following single oral doses of hydromorphone IR to healthy volunteers

Parameter	Dose of hydromorphone			90% CI of regression coefficient
	2 mg (n=26)	4 mg (n=26)	8 mg (n=25)	
Cmax (ng/ml)	1.25 ± 0.44	2.50 ± 0.96	5.38 ± 2.26	0.94, 1.13
Tmax (h)	0.73 ± 0.46	0.68 ± 0.42	0.74 ± 0.31	-0.09, 0.19
AUC(0-24h) (ng.h/ml)	4.28 ± 0.90	7.94 ± 1.65	15.0 ± 3.06	0.88, 0.95

Results given as mean ± sd
Regression coefficient for $\log_e$(dose)

Pairwise statistical comparison of pharmacokinetic parameters between dose levels confirmed dose proportionality of Cmax and AUC(0-24h) for hydromorphone, since 90% CIs for the differences between doses were within the (–20%, 25%) range (Table 9). The specified range for the confidence intervals is derived from European Union regulatory guidelines (EEC 1998).

Table 9. 90% CI from analysis of variance of dose proportionality comparisons

Parameter	90% confidence intervals[a]		
	4 mg - 2 mg	8 mg - 2 mg	8 mg - 4 mg
Cmax (ng/ml)	-10%, 15%	-7%, 19%	-8%, 17%
Tmax (h) [b]	-34%, 0%	-17%, 17%	0%, 37%
AUC(0-24h) (ng.h/ml)	-12%, -2%	-16%, -7%	-9%, 0%

[a] 90% CI presented for mean difference between doses, expressed as a percentage of the lowest dose mean. For Cmax and AUC(0-24h), CIs are based on the log-transformed data; back-transformed CIs are presented
[b] Based on median difference

The results indicated that the pharmacokinetics of oral immediate-release hydromorphone were linear over the 2-mg to 8-mg dose range studied.

4.3.2.2.3.2 FOOD EFFECT AND WITHIN-SUBJECT VARIABILITY

In an open, randomised, two-treatment (fed and fasted), three-way crossover study in 24 healthy Caucasian volunteers, the effect of food on the pharmacokinetics of hydromorphone after a single oral 8-mg dose of immediate-release hydromorphone (Durnin 2001b). Additionally, the within-subject variability in pharmacokinetics of hydromorphone after single fasted oral 8-mg doses of IR was assessed. The statistical analysis consisted of 90% confidence intervals (CI) for the differences between the fed and fasted regimens for bioequivalence assessment. Estimates of within and between subject variability were derived.

The plasma profiles of hydromorphone given without food were very similar to those previously observed, with rapid absorption into the systemic circulation reaching Cmax within 1 hour (Figure 5). For hydromorphone taken after food, absorption was less rapid, and Cmax was lower and occurred slightly later, although still within 1.5 hours of dosing (Figure 5, Table 10). Elimination was multiphasic for both regimens, but the initial rapid decline in plasma concentrations was less marked after food. A slower terminal elimination phase started about 8 hours after dosing. The terminal half-life of hydromorphone was similar for both regimens at around 15 hours. Although peak plasma concentrations were lower and occurred later after food, AUC increased by 30% indicating greater bioavailability of hydromorphone when taken with a meal. A similar increase in bioavailability after a high-fat meal has previously been documented with morphine (Gourlay 1989) and have been reported for other agents where mechanisms of the increase with food have been conjectured to be related to changes in the ability of the liver to metabolise highly-extracted drugs (Olsson 2001).

Figure 5. Mean plasma concentrations of hydromorphone in healthy male volunteers following single oral 8-mg doses of hydromorphone IR given with and without food

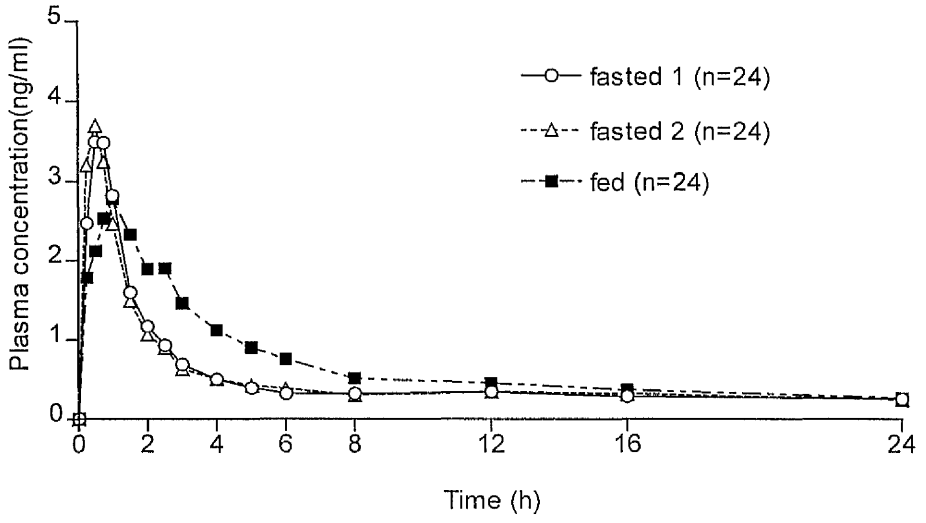


Table 10. Mean pharmacokinetic parameters of hydromorphone in healthy male volunteers following single oral 8-mg doses of hydromorphone IR given with and without food

Parameter	Fasted 1 (n=24)	Fasted 2 (n=24)	Fed (n=24)	90% CI for difference[a]
Cmax (ng/ml)	4.69 ± 1.71	4.78 ± 1.75	3.54 ± 1.38	-33%, -16%
Tmax (h)	0.63 ± 0.29	0.51 ± 0.21	1.31 ± 0.90	56%, 178%[b]
AUC(0-24h) (ng.h/ml)	12.2 ± 2.2	12.2 ± 2.7	16.5 ± 3.5	29%, 42%
AUC(0-∞) (ng.h/ml)	16.9 ± 3.5 (n=13)	16.9 ± 6.6 (n=15)	21.5 ± 5.3 (n=19)	13%, 37%

a 90% CI presented for mean difference, expressed as a percentage of the fasted treatment mean. For Cmax and AUC, CIs are based on the log-transformed data; back-transformed CIs are presented

b Based on median difference

Statistical analysis of the pharmacokinetic parameters after administration with and without food showed that the two regimens were not equivalent for AUC(0-24h) or Tmax (differences were 35% and 111%, respectively) and equivalence could not be confirmed for Cmax and AUC(0-∞) (differences were -25% and 24%, respectively). Within-subject variability (coefficient of variation), estimated from the two study periods with administration while fasted, was considerably less for AUC(0-24h) (about 10%) than for Cmax (about 30%).

The conclusion from this study is that there is a statistically significant effect of food on the pharmacokinetics of hydromorphone after dosing with immediate-release tablets, but the

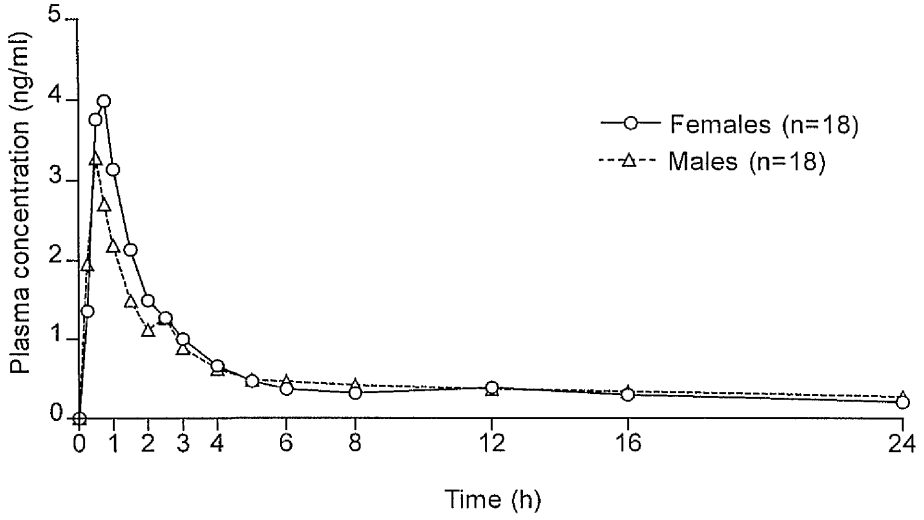
effects observed are not clinically relevant. The mean effect of food on bioavailability, at around 30%, is larger than the intra-individual variability. Nevertheless, this degree of variability is unlikely to be clinically relevant, given the multitude of other factors affecting analgesic effect. These other variables include mobility, wakefulness and dosing interval. In terms of possible safety concerns of the increased bioavailability, this is unlikely since the increase in plasma levels was not a product of increased Cmax, but rather elevated levels towards the end of a notional 4-hourly dosing interval. The delay in Tmax with food is also unlikely to be clinically relevant since one would assume that if a patient required rapid onset of effect of analgesia, they would probably not be eating a high fat meal at the time.

4.3.2.2.3.3 THE EFFECT OF SEX OF HEALTHY VOLUNTEERS ON PHARMACOKINETICS

In an open, parallel-group, single-dose study in 36 healthy Caucasian volunteers, 18 male and 18 female, aged 18 to 43 years, the pharmacokinetics of hydromorphone in male and female volunteers was compared after a single oral 8-mg dose of immediate-release hydromorphone (Durnin 2001c). The statistical analysis consisted of AUC and Cmax being log-transformed prior to analysis and 95% confidence intervals (CIs) for the differences between groups based on the two-sample t-statistic were calculated.

Plasma profiles were similar for males and females (Figure 6); hydromorphone was rapidly absorbed into the systemic circulation, reaching Cmax within 1 hour. Elimination was multiphasic; there was a rapid decline in plasma concentrations with a half-life of about 1.9 hours and some evidence of biliary recycling around 12 hours after dosing. This half-life value is similar to previously published values quoted as the terminal elimination half-life of hydromorphone (Vallner 1981) and most importantly, this half-life value is representative of the effective clinical activity of hydromorphone.

Figure 6. Mean plasma concentrations of hydromorphone in healthy male and female volunteers following a single oral 8-mg dose of hydromorphone IR



A slow terminal elimination phase started about 8 hours after dosing, but plasma levels of hydromorphone had already fallen to around 10% of Cmax by this time. Because of the secondary peaking, kel was poorly defined and could not always be calculated. The mean value of the terminal half-life for hydromorphone was around 17 hours in the male volunteers (13 of 18) and 13 hours in the female volunteers (9 of 18).

The effect of sex on the pharmacokinetics of hydromorphone was an increase in Cmax (30%) but a difference of less than 2% in AUC(0-24h) in the female group compared to the male group (Table 11). From an incomplete dataset, terminal rate constant was 39% greater for the female group compared to the male group; however the difference in AUC(0-∞) was 0.5%. No difference was observed between groups for Tmax.

Table 11. Mean pharmacokinetic parameters of hydromorphone in healthy male and female volunteers following a single oral 8-mg dose of hydromorphone IR

Parameter	Female (n=18)	Male (n=18)	95% CI[a]
Cmax (ng/ml)	5.12 ± 3.07	4.09 ± 2.12	-9%,85%
Tmax (h)	0.75 ± 0.31	1.01 ± 0.82	-49%,25%[b]
AUC(0-24h) (ng.h/ml)	13.4 ± 4.7	13.0 ± 3.5	-17%,25.1%

Results presented as mean ± sd

[a] 95% CI presented for mean difference, expressed as a percentage of the male group mean. For Cmax and AUC, CIs are based on the log-transformed data; back-transformed CIs are presented

[b] Based on median difference

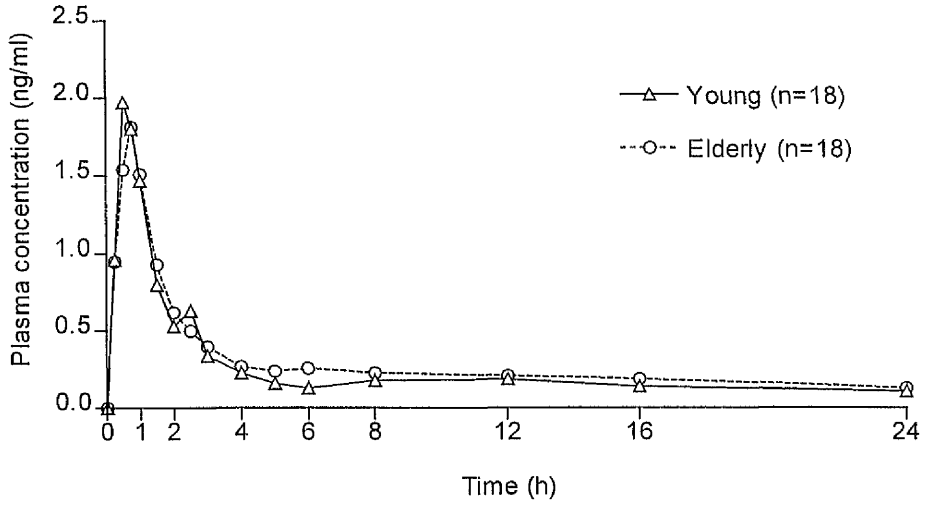
This study demonstrated that sex had little effect on the pharmacokinetics of oral immediate-release hydromorphone. There were no significant differences in AUC(0-24h) between the two groups. The difference in Cmax between the two groups is similar to the effect previously documented with morphine (McQuay 1990) and is not considered to be clinically relevant.

4.3.2.2.3.4 AGE EFFECT

In an open, parallel-group, single-dose study in 36 healthy Caucasian volunteers, 18 young (age range 18 to 38 years) and 18 elderly (age range 65 to 74 years) were enrolled to study the effect of age on the pharmacokinetics of hydromorphone after a single oral 4-mg dose of immediate-release hydromorphone (Durnin 2001d). For the statistical analysis, AUC and Cmax were log-transformed prior to analysis and 95% confidence intervals (CIs) for the differences between groups based on the two-sample t-statistic were calculated.

Plasma profiles were similar for young and elderly subjects; hydromorphone was rapidly absorbed into the systemic circulation, reaching Cmax within 1 hour (Figure 7). Elimination was multiphasic; there was a rapid decline in plasma concentrations with a half-life of about 1.6 hours for the young and 1.9 hours for the elderly with some evidence of biliary recycling 8 to 12 hours after dosing.

Figure 7. Mean plasma concentrations of hydromorphone in healthy young and elderly volunteers following a single oral 4-mg dose of hydromorphone IR



A slow terminal elimination phase started about 8 hours after dosing, but plasma levels of hydromorphone had already fallen to around 9% and 13% of Cmax by this time for the young and elderly groups, respectively. Because of the secondary peaking and the comparatively low 4-mg dose used in this study, kel was poorly defined and could not always be calculated. The mean value of the terminal half-life for hydromorphone was around 12 hours in the young volunteers (8 of 18) and 15 hours in the elderly volunteers (8 of 18).

The effect of age on the pharmacokinetics of hydromorphone was a modest increase in AUC(0-24h) (11%) but a reduction in Cmax (14%) in the elderly compared to the young (Table 12). No difference in Tmax was observed. From an incomplete dataset, terminal rate constant was reduced by 8% and AUC(0-□) was increased by 10% for the elderly group compared to the young group.

Table 12. Mean pharmacokinetic parameters of hydromorphone in healthy young and elderly volunteers following a single oral 4-mg dose of hydromorphone IR

Parameter	Young (n=18)	Elderly (n=18)	% mean diff.	95% CI[a]
Cmax (ng/ml)	2.49 ± 0.88	2.21 ± 1.06	-14%	-36%, 16%
Tmax (h)	0.74 ± 0.48	0.75 ± 0.34	0%	0%, 34%[b]
AUC (0-24h) (ng.h/ml)	6.1 ± 1.3	7.0 ± 2.4	11%	-9%, 34%

Results presented as mean ± sd

[a] 95% CI presented for mean difference, expressed as a percentage of the young group mean. For Cmax and AUC(0-24h), CIs are based on the log-transformed data; back-transformed CIs are presented

[b] Based on median difference

Overall, age had little effect on the pharmacokinetics of hydromorphone. The reduction of 14% in Cmax and increase of 11% in AUC(0-24h) in the elderly are not considered to be clinically relevant. Data from this study therefore indicate that there is no need to adjust the starting dose of oral immediate-release hydromorphone in the elderly.

4.3.2.2.3.5 RENAL IMPAIRMENT

An open, parallel-group, single-dose study of 23 volunteers examined the effect of renal impairment on the pharmacokinetics of hydromorphone (Durnin 2001e). Volunteers were divided into three categories of renal impairment according to serum creatinine values which were used to derive a creatinine clearance value using the Cockcroft Gault equation

(Cockcroft 1976). Seven volunteers were recruited with normal renal function (creatinine clearance (Cl_{Cr}):>80 ml/min), eight with moderate renal impairment (Cl_{Cr}: 40-60 ml/min) and eight with severe renal impairment (Cl_{Cr}: <30 ml/min, including those receiving dialysis). The statistical analysis of the data involved analysis of covariance with factors for renal group and sex and a covariate for age on log-transformed Cmax and AUC with corresponding 95% confidence intervals (CIs).

In the volunteers with normal renal function, hydromorphone was rapidly absorbed reaching Cmax within 1 hour (Figure 8). Concentrations of hydromorphone in subjects with moderate renal impairment were higher than in subjects with normal renal function. In the severe renal impairment group, Cmax was similar to normal volunteers but occurred later and was followed by more sustained plasma levels of hydromorphone. Elimination was multiphasic in all groups; there was a rapid decline in plasma concentrations for the groups with normal and moderately-impaired renal function, a slower decline in the severely-impaired group, followed by a slow terminal elimination phase for all groups (Table 13).

Figure 8. Mean plasma concentrations of hydromorphone in volunteers with normal renal function and moderate and severe renal impairment following a single oral 4-mg dose of hydromorphone IR

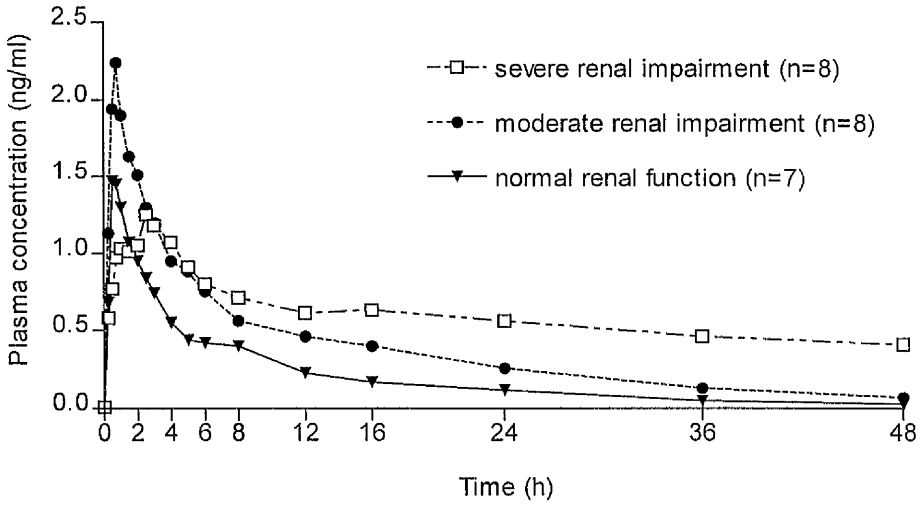


Table 13. Mean pharmacokinetic parameters of hydromorphone in volunteers with normal renal function and moderate and severe renal impairment following a single oral 4-mg dose of hydromorphone IR

Parameter	Renal function		
	Normal (n=7)	Moderate impairment (n=8)	Severe impairment (n=8)
Cmax (ng/ml)	1.8 ± 0.6	2.6 ± 1.0	1.4 ± 0.4
Tmax (h)	0.68 ± 0.19	0.84 ± 0.50	1.96 ± 0.98
AUC (0-t) (ng.h/ml)	8.5 ± 3.1	16.9 ± 6.3	26.8 ± 7.5
AUC (0-∞) (ng.h/ml)	11.3 ± 2.7	20.8 ± 5.7	50.2 ± 26.7
kel (/h)	0.077 ± 0.057	0.050 ± 0.012	0.021 ± 0.012
t½ (h)	14.8 ± 11.3	14.4 ± 3.5	39.4 ± 16.0

Results given as mean ± sd

Hence, renal impairment produced changes in the pharmacokinetics of hydromorphone. The increased plasma levels of hydromorphone in the group with moderate renal impairment resulted in 2-fold increases in mean Cmax and AUC (95% CI: 43%,196%). For the group with severe renal impairment, hydromorphone appeared to be both more slowly absorbed and metabolised, with more sustained levels of hydromorphone, resulting in a 4-fold increase in AUC (95% CI: 168%,502%).

Two subjects with severe renal impairment were given a 4-hour haemodialysis about 48 hours after dosing; post-dialysis plasma levels of hydromorphone were approximately 40% of pre-dialysis levels.

The study concluded that the effects of renal impairment on the pharmacokinetics of hydromorphone were increases in AUC with decreasing renal function. This is similar to the findings of studies of the effects of renal impairment on the pharmacokinetics of morphine (Osborne 1994) and the effects may be attributable to the effects of renal dysfunction on hepatic clearance of drug (Terao 1985). The ratio of hydromorphone AUCs for normal volunteers and subjects with moderate or severe renal impairment was approximately 1:2:4, respectively. Haemodialysis was effective at reducing plasma levels of hydromorphone.

Therefore, patients with moderate renal insufficiency should be started on a reduced dose and closely monitored during dose titration. In patients with severe renal insufficiency an increased dosing interval should also be considered and these patients should in addition be

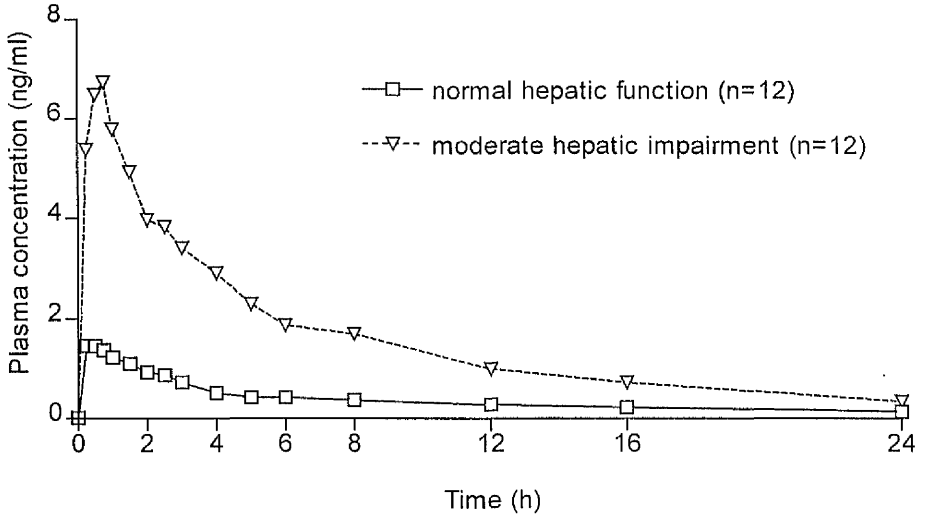
monitored during maintenance therapy. Published reports suggest that hydromorphone is reasonably well tolerated in patients with impaired renal function (Lee 2001).

4.3.2.2.3.6 HEPATIC IMPAIRMENT

An open, parallel-group, single-dose study in 24 volunteers, 12 with normal hepatic function and 12 with moderate hepatic impairment was performed to compare the pharmacokinetics of hydromorphone in the two groups (Durnin 2001f). Moderate hepatic impairment was defined as a Child-Pugh score of 7 to 9 (Child-Pugh score is derived by scoring ascites, encephalopathy, bilirubin, albumin and prothrombin time: 5 points = normal hepatic function to 10 points = severe hepatic impairment [Pugh 1973]). The cause of hepatic impairment was alcoholic cirrhosis in all cases. For the statistical analysis of the data, AUC and Cmax were log-transformed prior to analysis and 95% confidence intervals (CIs) for the differences between groups were based on the two-sample t-statistic.

Hydromorphone was rapidly absorbed in both groups, reaching Cmax within 1 hour (Figure 9). Plasma concentrations of hydromorphone were higher in the subjects with moderate hepatic impairment than in subjects with normal hepatic function. This was probably a consequence of reduced first-pass metabolism.

Figure 9. Mean plasma concentrations of hydromorphone in volunteers with normal or moderately-impaired hepatic function following a single oral 4-mg dose of hydromorphone IR



Elimination was multiphasic in both groups with an initial rapid decline in plasma concentrations followed by a slower elimination phase. Furthermore the terminal

elimination characteristics of hydromorphone were similar, i.e. reduced hepatic function did not have any major effect on elimination of hydromorphone.

The effect of hepatic impairment on the pharmacokinetics of hydromorphone was shown to be a marked 4-fold increase in both Cmax and AUC (Table 14). No difference in Tmax was observed. No major changes in elimination were observed; the apparent differences may be a consequence of the higher plasma concentrations in hepatic impairment allowing the elimination phase to be better defined.

Table 14. Mean pharmacokinetic parameters of hydromorphone in volunteers with normal or moderately-impaired hepatic function following a single oral 4-mg dose of hydromorphone IR

Parameter	Hepatic function group		% mean difference	95% CI[a]
	Normal (n=12)	Moderate impairment (n=12)		
Cmax (ng/ml)	2.0 ± 1.3	8.3 ± 4.2	303%	150%, 551%
Tmax (h)	0.77 ± 0.49	1.09 ± 1.14	0%	-65%, 65%[b]
AUC (0-48) (ng.h/ml)	10.4 ± 2.3	41.8 ± 14.7	285%	192%, 409%
AUC (0-∞) (ng.h/ml)	11.6 ± 2.0	43.2 ± 14.8	254%	173%, 359%
kel (/h)	0.064 ± 0.018	0.090 ± 0.022	40%	13%, 66%
t½ (h)	11.5 ± 3.0	8.3 ± 2.5	-	-

Results presented as mean ± sd

[a] 95% CI presented for mean difference, expressed as a percentage of the normal group mean. For Cmax and AUC, CIs are based on the log-transformed data; back-transformed CIs are presented

[b] Based on median difference

The study showed that the effect of moderate hepatic impairment on the pharmacokinetics of hydromorphone is an increase in hydromorphone bioavailability, as demonstrated by the higher plasma concentrations of hydromorphone and the 4-fold increases in Cmax and AUC, compared to the group with normal hepatic function. Therefore, patients with moderate hepatic insufficiency should be started on a reduced dose and closely monitored during dose titration.

4.3.2.2.4 Controlled-release formulation

4.3.2.2.4.1 DOSE PROPORTIONALITY

In a study of 12 healthy young volunteers, the single-dose pharmacokinetics of the controlled-release formulation were compared with the immediate release tablets (Angst 2001). The findings are presented in Table 15.

Table 15. Pharmacokinetic indices after administration of immediate- and controlled-release hydromorphone

Dose	Peak plasma concentration (ng/ml)	Time to peak Cp (h)	First-time Cp > 50% Peak (h)[a]	Last-time Cp > 50% peak (h)[b]	Duration Cp > 50% peak Cp (h)[c]
8 mg IR	4.74 ± 1.76	0.8 (0.8 – 1.0)	0.4 ± 0.2	1.6 ± 0.8	1.1 ± 0.7
8 mg CR	0.77 ± 0.33	12.0 (9.0 – 13.5)	5.4 ± 1.7	30.9 ± 10.6	24.2 ± 10.3
16 mg CR	1.45 ± 0.43	15.0 (12.0 – 18.0)	6.1 ± 2.3	31.5 ± 9.4	21.6 ± 8.1
32 mg CR	2.41 ± 0.85	16.5 (12.0 – 21.0)	5.5 ± 1.8	35.8 ± 6.9	26.5 ± 7.5

Data are mean ± SD or median and interquartile range.
a This value represents the time after dosing when the plasma concentration first rises to 50% of the Cmax
b This value represents the time after dosing when the plasma concentration first falls to 50% of the Cmax
c This value represents the amount of time that the plasma concentration remains at levels greater than 50% of Cmax.

The controlled-release formulation clearly achieves a very flat profile of release compared with the immediate-release form and appears to be of practical use for once-daily dosing.

In a study of 31 young healthy volunteers (Velagapudi 2001a), dose-proportional pharmacokinetics were confirmed over the tablet strengths of 8, 16, 32 and 64 mg. Additionally, other pharmacokinetic data were consistent with those reported from the Angst study (see Table 16). Naltrexone doses were co-administered with hydromorphone to protect the subjects from severe adverse pharmacological effects of administration of hydromorphone.

Table 16. Pharmacokinetic data from study of 31 young healthy volunteers. Mean (± SD)

Pharmacokinetic Parameters	8 mg	16 mg	32 mg	64 mg
Tmax (h)	16.0 (7.2)	16.8 (5.4)	15.7 (5.4)	17.4 (5.7)
$T_{1/2}$ (h)	10.6 (4.3)	10.3 (2.4)	11.0 (3.2)	10.9 (3.8)
Cmax (ng/mL)	0.929 (1.01)	1.69 (0.78)	3.25 (1.37)	6.61 (1.75)
AUC 0-48 (ng.h/mL)	18.1 (5.8)	36.5 (11.3)	72.2 (24.3)	156 (30.6)
AUC 0-INF (ng.h/mL)	19.5 (5.9)	40.8 (13.7)	80.3 (29.6)	178.7 (35.2)

4.3.2.2.4.2 BIOAVAILABILITY

The Angst study was reported in a separate abstract where the absolute bioavailability data were presented (Drover 1999). These data were derived from the pharmacokinetics of an 8-mg dose of intravenous hydromorphone which was administered during a preceding treatment phase of this study. The absolute bioavailability of the controlled-release formulation ranged from 22.0% to 25.9% for the three doses of controlled-release tablets that were tested. These figures compare with 18.7% for the immediate-release tablet. These differences are not statistically significant, however. A further study comparing the AUC of the controlled-release formulation versus the immediate-release form after dosing to steady state confirmed greater bioavailability with the CR form (Shah 1997). The respective values for AUC (not specified, but presumably 0 – 24 hours) were 45.6 and 41.7 ng.h/ml. This study also measured hydromorphone-3-glucuronide and reported similar levels of the metabolite with both formulations, but greater parent drug:metabolite ratios with the CR formulation which is further evidence for greater bioavailability. Steady state was achieved by day two of the four-day study.

The trend towards increased bioavailability with controlled-release formulation dosing may be a result of relatively greater absorption of the dose from the lower GI tract. This assumes that at the time of peak plasma concentration, the OROS tablet has progressed significantly further down the GI tract than the area of absorption of a dissolved immediate-release tablet (which is presumably the duodenum and proximal jejunum). Another factor that could account for a greater bioavailability after single doses of the controlled-release formulation is the effect of food on bioavailability (see above). The time of fasting in healthy volunteer studies tends to range from two to four hours after dosing. During this time period, the vast majority of absorption following administration of an immediate-release tablet would have taken place. In contrast, the absorption of hydromorphone in solution, released from the controlled release formulation, would still be taking place around the time of meals being administered to the volunteers (conventionally, around four to eight hours after dosing). Therefore, the increased bioavailability observed with the controlled-release formulation could be an artefact of the timing of meals in single dose pharmacokinetic studies.

4.3.2.2.4.3 FOOD EFFECT

In a study of 27 healthy volunteers (Velagapudi 2001b), 16-mg single doses of the controlled-release formulation of hydromorphone were given in both the fed and fasted state to assess the effect of food on the pharmacokinetics of the controlled-release formulation. While the Tmax was significantly earlier ($p<0.01$) for (fed) treatment B (12.0 h) compared with (fasting) treatment A (16.0 h), Cmax values for treatment B (1.352 ng/ml) were within 20% of those for treatment A (1.107 ng/ml). The AUCs were within 10% for treatment B vs treatment A (AUC 0-48: 30.20 vs 31.12 ng.h/ml, and AUC0-INF: 36.09 vs 38.84 ng.h/ml, respectively). The 90% confidence interval for lnAUC 0-INF (fed vs fasted) was 81.9% to 99.4%. Thus, the results suggested that the effect of food is not likely to be clinically significant.

4.4 Acute pain models

4.4.1 Placebo-controlled studies with oral hydromorphone in acute pain

Three placebo-controlled studies involving oral hydromorphone in patients with a variety of acute or chronic painful conditions have demonstrated the analgesic superiority of hydromorphone over placebo. Two studies compared two dosage levels of oral hydromorphone (Table 17).

One of these studies (Goldberg 1965) was a multiple-dose study over a period of between 2 days and 4 weeks. In this trial, in which 2 mg or 4 mg oral hydromorphone was given 4 to 6 hourly both doses of hydromorphone were shown to be analgesically superior to placebo as measured by categorical scales of pain relief. The higher dose (4 mg) was more effective than the lower dose (2 mg).

One trial (Jain 1989) compared the efficacy of a single dose of 5 mg with 10 mg hydromorphone given as an oral solution in patients with moderate or severe post-operative pain. In all measures of analgesia, hydromorphone was superior to placebo and 10 mg was superior to 5 mg. In the active groups, onset of analgesia was prompt and peaked around 3 hours post-dose.

In both of these studies, oral hydromorphone was well tolerated at all doses, although the occurrence of unwanted effects tended to be less frequent with the lower dose than with the higher dose. Somnolence and drowsiness were the most frequently reported adverse events. There were no reports of serious adverse events. These studies serve to support the analgesic potency and tolerability of oral hydromorphone on a dose-related basis.

A further placebo-controlled study assessed the value of oral hydromorphone (2 mg) plus oral lorazepam (2 mg) in reducing pain and anxiety in patients undergoing outpatient bone marrow biopsy and aspiration (Wolanskji 1998). There was no difference between placebo and hydromorphone plus lorazepam for these parameters.

Table 17. Placebo-controlled studies with oral hydromorphone in acute pain

Author; year; country	Indication; dose of hydromorphone (H) (mg)	Design; number of patients; Duration	Comparator; dose (mg)	Global clinical outcome	
				Efficacy	Tolerability
Goldberg 1965; USA	Acute trauma; 2 mg or 4 mg qds	db; 30; 2 days to 4 weeks	Placebo (P)	H4 mg >H2 mg >P	P =H2 mg ?>H4 mg
Jain 1989; USA	Post-operative pain; 5 mg or 10 mg oral solution as single dose	db; 61; 6 hours	Placebo (P)	H10 mg >H5 mg >P	P ≥H5 mg ≥H10 mg
Wolanskyi 1998; USA	Bone marrow biopsy and aspiration; 2 mg single dose (H) plus 2 mg oral lorazepam (L)	db; 25; 24 hours	Placebo (P)	P= H+L	Not stated

qds = four times daily; db = double blind; > = descriptively or statistically better than; ≥ = trend in favour of; = = equivalent

4.4.2 Comparative clinical studies between oral hydromorphone and other analgesics in acute pain

Two clinical studies have compared the effect of oral hydromorphone with the comparator being morphine in one case and meperidine (pethidine) in the other (Table 18). These studies have indicated a morphine:hydromorphone dose equivalence ratio of 6-7.5:1 in patients with post-operative pain and that both exhibited unwanted effects typical of opioid drugs. Further, hydromorphone was analgesically superior to meperidine (pethidine) in oral surgical pain.

Turek (1987) compared the effect of a 5 mg or 10 mg oral solution of hydromorphone given as a single dose, with that of 30 mg or 60 mg of morphine using the same formulation and

route, in 21 patients with moderate to severe post-operative pain. The results indicate that in terms of analgesic potency, measured by categorical scales, hydromorphone 5 mg was therapeutically equivalent to 30 mg morphine and 10 mg to 60 mg respectively. This suggests a potency ratio of 6:1 for morphine: hydromorphone given by the oral route.

Nasits (1969) compared the efficacy of two different dosages of oral hydromorphone with meperidine (pethidine) in 39 patients with pain following oral surgery. Dosages of hydromorphone were 1.5 or 2.0 mg and that for meperidine (pethidine) was 100 mg, all given 3 hourly for a maximum of 4 doses. Using measures of pain relief as being "complete", "partial" or "none", a greater proportion of patients receiving 1.5 mg/dose of hydromorphone reported complete pain relief than those receiving 2 mg/dose of hydromorphone or 100 mg/dose of meperidine (pethidine). Side effects comprising nausea, vomiting, headache, dizziness and sedation were greater with the higher dose of hydromorphone than the lower dose. Overall there were slightly fewer side effects with meperidine (pethidine).

Table 18. Comparative clinical studies between oral hydromorphone and other analgesics in acute pain

Author; year; country	Indication; dose of hydromorphone (H) (mg)	Design; number of patients; duration	Comparator; dose (mg)	Global clinical outcome	
				Efficacy	Toler-ability
Turek 1987; USA	Post-operative pain; H5 mg or H10 mg single dose (oral solution)	db; 21; <1 day	Morphine M30 mg or M60 mg single dose (oral solution)	H5 mg = M30 mg H10 mg = M60 mg	"Usual type"
Nasits 1969; ?USA	Oral surgical pain; H1.5 mg or H2.0 mg 3 hourly for max 4 doses	db; 39; <1 day	Meperidine (pethidine) (Mp); 100 mg 3 hourly for max 4 doses	H1.5 mg ≥H2.0 mg ≥Mp	Mp ≥M1.5 mg ≥M2.0 mg

db = double blind; xo = cross-over; CRH = controlled-release hydromorphone; > = descriptively or statistically better than; ≥ = trend in favour of; = = equivalent to

4.5 Chronic pain models

4.5.1 Placebo-controlled study with oral hydromorphone in chronic pain

A single placebo-controlled study involving oral hydromorphone in patients with chronic painful conditions have demonstrated the analgesic superiority of hydromorphone over placebo. The study compared two dosage levels of oral hydromorphone (Table 19). It was a multiple-dose study over six days. In this study in which 2-mg or 4 mg oral hydromorphone was given 4-hourly both doses of hydromorphone were shown to be superior to placebo as measured by categorical scales of pain relief. The higher dose (4 mg) was more effective than the lower dose (2 mg) in a dose-related fashion. The study was also a crossover design which enabled a rank order of pain relief scores to be made. There was clear discrimination of effect consistent with the dose-response findings.

Table 19. Placebo-controlled studies with oral hydromorphone in acute pain

Author; year; country	Indication; dose of hydromorphone (H) (mg)	Design; number of patients; Duration	Comparator; dose (mg)	Global clinical outcome	
				Efficacy	Tolerability
Cass 1965; USA	Chronic pain (bone/joint); 2 mg or 4 mg 4 hourly	db, xo; 29; 6 days	Placebo (P)	H4 mg >H2 mg >P	P =H2 mg >H4 mg

qds = four times daily; db = double blind; > = descriptively or statistically better than; ≥ = trend in favour of; = = equivalent

In this study, oral hydromorphone was well tolerated at both doses, although the occurrence of unwanted effects tended to be less frequent with the lower dose than with the higher dose. Drowsiness was the most frequently reported adverse event. There were no reports of serious adverse events. This study supports the analgesic potency and tolerability of oral hydromorphone on a dose-related basis.

4.5.2 Comparative clinical studies between oral hydromorphone and other analgesics in chronic pain

Two clinical studies have compared the effect of oral hydromorphone with the control treatment being morphine in one and oxycodone in the other (Table 20).

Table 20. Comparative clinical studies between oral hydromorphone and other analgesics in chronic pain

Author; year; country	Indication; dose of hydromorphone (H) (mg)	Design; number of patients; duration	Comparator; dose (mg)	Global clinical outcome	
				Efficacy	Toler-ability
Moriarty 1999; UK	Stable cancer pain; CRH 4 mg given 12 hourly	db 100; 3 days	Controlled-release morphine (CRM) 30 mg given 12 hourly	CRH = CRM 1:7.5 analgesic potency	CRH = CRM (overall)
Hagen 1997; Canada	Stable cancer pain; CRH 30± 6 mg/day given 12 hourly	db; xo; 44; 7 days	Controlled-release oxycodone (CRO) 124 ± 22 mg/day given 12 hourly	CRH = CRO	CRH > CRO (drowsiness)

db = double blind; xo = cross-over; CRH = controlled-release hydromorphone; > = descriptively or statistically better than; ≥ = trend in favour of; = = equivalent to

Moriarty (1999) compared the effect of a controlled-release oral formulation of hydromorphone 4 mg given 12 hourly for 3 days with 30 mg of controlled-release morphine given orally every 12 hours in 100 patients whose cancer pain had been stabilised on controlled-release morphine. Both treatments controlled pain satisfactorily. The principal measure of efficacy in this study was the number of occasions that escape analgesia was used. The frequency of use of escape analgesia was low in each group with no differences between groups for this measure nor for any pain measure or for patient preference. The authors suggest that the morphine:hydromorphone analgesic potency ratio by the oral route is 7.5:1. Both medications were well tolerated with no significant differences between them for the degree of nausea and sedation.

In a crossover study in 44 patients with stable cancer pain, Hagen (1997) compared the effect of oral controlled-release hydromorphone (mean dose 30 mg/day, given 12 hourly) with that of oral controlled-release oxycodone (mean dose 124 mg/day, given 12 hourly). Using visual analogue scales (VAS) and categorical scales to measure pain and use of rescue analgesia over a 7-day study period, both treatments were shown to be effective with no differences between them throughout any 24-hour period. VAS scores for sedation and nausea were similarly low for each treatment although drowsiness was reported significantly more frequently ($p=0.016$) with oxycodone.

5. Clinical studies

5 Clinical studies

The essential features of the clinical studies conducted with hydromorphone are summarised in Table 21 below.

Table 21. Study features

Title, country	Design	Dose regimen, route, duration of treatment	Number of patients, diagnosis, comparator	Evaluations
Placebo controlled				
Single dose in postoperative pain UK, F, NL	DBPG	2, 4 and 6 mg Single oral dose of IR tablet	205 post primary knee arthroplasty Placebo	SPID, adverse events
Active controlled				
Multiple dose study in postoperative pain UK, F, NL, Eire	DBPG	3 hourly-as-required oral doses of 2, 4 and 6 mg of IR tablet Up to 48 hours	271 post primary knee arthroplasty, Morphine 20 mg oral	Mean pain score (by AUC), adverse events
Multiple dose study in cancer pain UK, Es, Fr, NL, De, Sw, Be, Can	DBPG	IR phase: 4-hourly oral dosing (12-108 mg/day) until dose-stable pain control achieved (2- 9 days). CR phase: Once daily dosing (16-96 mg/day) until dose-stable pain control achieved (10-15 days).	201 patients with cancer pain. IR phase: 4-hourly oral morphine (60-540 mg/day). CR phase: 12-hourly oral morphine (60-520 mg/day).	"Worst pain", other pain scores through BPI, adverse events

DB = double-blind, PG = parallel group, OL= open-label, SPID = sum of pain intensity differences, BPI = Brief pain Inventory

5.1 Formulations studied

In the two studies of post-operative pain, the hydromorphone immediate-release tablet only was used. In the cancer pain study, the immediate-release tablet was used in the initial phase of the study. In the second phase of the cancer pain study, the once-daily controlled-release hydromorphone tablet was used. Corresponding control treatments were used in all of the studies.

5.2 Placebo-controlled single-dose study in postoperative pain

5.2 Placebo-controlled single-dose study in postoperative pain

5.2.1 Study summary

The study was entitled, "A double-blind, single dose, placebo-controlled dose-ranging investigation into the efficacy and tolerability of an immediate- release tablet formulation of hydromorphone in the treatment of acute post-operative pain". The co-ordinating investigator was Professor D Rowbotham, of Leicester Royal Infirmary, Infirmary Road, Leicester, LE1 5WW.

The objectives of the study were i) to compare the efficacy of three single doses (2, 4 and 6 mg) of hydromorphone with placebo during the post-operative recovery of patients who undergo primary knee replacement surgery; each individual patient received only one dose administered orally as an immediate-release tablet and ii) to evaluate the tolerability of the three single doses (2, 4 and 6 mg) of hydromorphone and placebo during the post-operative period.

The methodology of the study was multicentre, double blind, placebo-controlled, parallel group, dose ranging. Assessments were made at baseline (0 hours) and at 0.5, 1, 2, 3, 4, 5 and 6 hours after dosing with study medication.

The number of patients planned for the study was 200; 50 in each of the four treatment groups. Two-hundred-and-five patients entered the study, 51 received hydromorphone 2 mg, 49 hydromorphone 4 mg, 51 hydromorphone 6 mg and 54 placebo. 204 patients were included in the analysis of the principal measure of efficacy. The sample population was hospital inpatients who required post-operative analgesic therapy for pain following primary knee arthroplasty.

The measures of efficacy were pain at rest, pain on movement, and time to pain at rest returning to the baseline value. The measures of safety were adverse events and sedation.

The principal measure of efficacy was the sum of the pain intensity differences (SPID) for pain at rest. Hydromorphone 4 and 6 mg were significantly more effective in reducing pain at rest compared with placebo ($p=0.03$ for both comparisons). There was no statistically significant difference between hydromorphone 2mg and placebo. The adjusted means for

SPID were -2.3, -5.2, -4.4 and 0.6 for hydromorphone 2, 4 and 6 mg and placebo, respectively.

Results were similar for the analyses of SPID for pain on movement. Hydromorphone 4 and 6mg were significantly more effective compared with placebo ($p=0.04$ for both comparisons). There was no statistically significant difference between hydromorphone 2 mg and placebo ($p=0.60$). The adjusted means for SPID were –1.3, -5.6, -3.9 and –0.2 for hydromorphone 2, 4 and 6 mg and placebo, respectively.

In the analyses at individual time-points for pain at rest, hydromorphone 6 mg was more effective in reducing pain than placebo at hour 1 and 2 ($p<0.05$); both hydromorphone 4 and 6mg were more effective than placebo at hour 3 ($p<0.01$). For pain on movement, all hydromorphone doses were more effective than placebo at hour 1 ($p<0.05$ for 2mg and $p<0.01$ for 4 and 6 mg) and hydromorphone 4 mg and 6 mg were more effective than placebo at hours 2 and 3 ($p<0.05$).

For the analysis of the time to pain at rest returning to the baseline value, the overall treatment group comparison was not statistically significant ($p=0.07$), although the pairwise comparison between hydromorphone 6mg and placebo was significant ($p=0.013$). The Kaplan-Meier estimates for time for pain at rest returning to baseline value were 165.4, 191.6, 209.5 and 109.7 minutes for the hydromorphone 2, 4 and 6mg groups and the placebo groups respectively. The number of patients reporting pain values returning to the original baseline was over 60% in all four treatment groups, with highest incidence rate in the placebo group (77%) and the lowest in the hydromorphone 6mg group (63%).

Adverse events were reported by 11 (22%) patients, 15 (31%) patients, 17 (33%) patients and 15 (28%) patients, respectively; there was no statistically significant difference between the four groups in the proportion of patients who reported adverse events. Most adverse events were mild and the relationship to therapy was unlikely or none for approximately 50% of the reported adverse events. Nausea, vomiting and pyrexia were the most common adverse events. Generally, the reports of nausea and vomiting were assessed by the investigator as being probably or possibly related to treatment, whilst reports of pyrexia were assessed as having an unlikely or no relationship to treatment. This is not unexpected as nausea and vomiting are commonly reported side effects associated with opioids.

Including adverse events ongoing at randomisation, similar numbers of patients in the hydromorphone 4 mg, 6 mg and placebo groups experienced adverse events commonly reported with morphine (13, 11 and 12 patients, respectively); patients in the hydromorphone 2 mg group reported fewer of these events (7 patients). Five patients withdrew from the study due to adverse events (one in the hydromorphone 2-mg group, three in the 4-mg group and one in the placebo group).

Assay sensitivity, the ability to demonstrate the statistically significant activity of an analgesic agent compared to placebo or to another agent, represents a noteworthy achievement for any analgesic study (Schachtel, 1991). Hydromorphone 4 mg and 6 mg were statistically significantly more efficacious than placebo in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery. The tolerability of the three hydromorphone doses was comparable to placebo. These findings confirm impressions gained from more than 50 years of clinical use in North America. Namely, hydromorphone is an effective and safe analgesic in the treatment of acute pain.

5.2.2 Introduction

This was the first of two studies addressing the time at which patients cease using parenteral opioids by PCA for the management of severe postoperative pain, referred to above as the "analgesic gap".

Patients recovering from primary knee arthroplasty suffer severe pain. In order to test an oral opioid analgesic in this setting, it was necessary to delay the beginning of the study period to the time when patients had their pain control stabilised with the use of morphine patient controlled analgesia (PCA) and when the patient was able to tolerate oral intake. The interval selected was 18 – 48 hours after the patient left the operating theatre. This was judged to include the probable minimal time for a patient to fulfil the criteria and not be of such a long duration as to result in recovery from postoperative pain to the degree that oral opioid analgesia would no longer be appropriate.

The PCA was controlled in so much as this had to use morphine, and there was an element of control in the use of post-operative use of non-steroidal anti-inflammatory drugs (NSAID) whereby only a fixed dose and route of diclofenac (100 mg p.r.) could be used.

However, the use of NSAIDs was optional. This was to allow for the differences in preference between investigators, centres and countries. The type of anaesthetic procedure was not controlled, since this was felt to be impracticable in the setting of a multicentre, multinational study. The scope of anaesthetic procedure included regional techniques, such as spinal anaesthesia and nerve blocks, but these had to complete at the time that the patient left the operating theatre. The variability that this was bound to introduce should have been lessened in its impact through the minimum 18 hour PCA period bringing patients back to a more consistent baseline. Additionally, testing for the motor and sensory effects of regional techniques was designed to prevent residual effects of these measures affecting measures in the period of the study following randomisation. A minimum degree of pain at baseline assessment was not included as a selection criterion.

The study was designed as multicentre and multinational in order to allow for recruitment of the 200 patients estimated to be required in a reasonable interval.

The doses used in the study were based on published guidelines (American Pain Society, 1993). In fact, the study was originally designed to examine 2, 4 and 8-mg doses of hydromorphone, but concerns were raised by the UK regulatory agency medical reviewer as to the risk of an 8-mg dose in this setting. His concerns were based on an equipotency ratio of 7.5, which would make an 8-mg dose of hydromorphone equivalent to 60 mg of morphine.

5.2.3 Objectives

Firstly, to compare the efficacy of three single doses (2, 4 and 6 mg) of hydromorphone with placebo during the post-operative recovery of patients who undergo primary knee replacement surgery, and secondly, to evaluate the tolerability of the three single doses (2, 4 and 6 mg) of hydromorphone compared with placebo.

5.2.4 Methods

This was a multicentre, phase II, randomised, double-blind, placebo-controlled, parallel-group study. The study was conducted at 24 centres in the United Kingdom, Netherlands and France; these hospitals had departments/units specialising in the

management of acute pain. The planned sample size was 200 patients (50 patients in each of the four treatment groups).

5.2.4.1 Patient selection

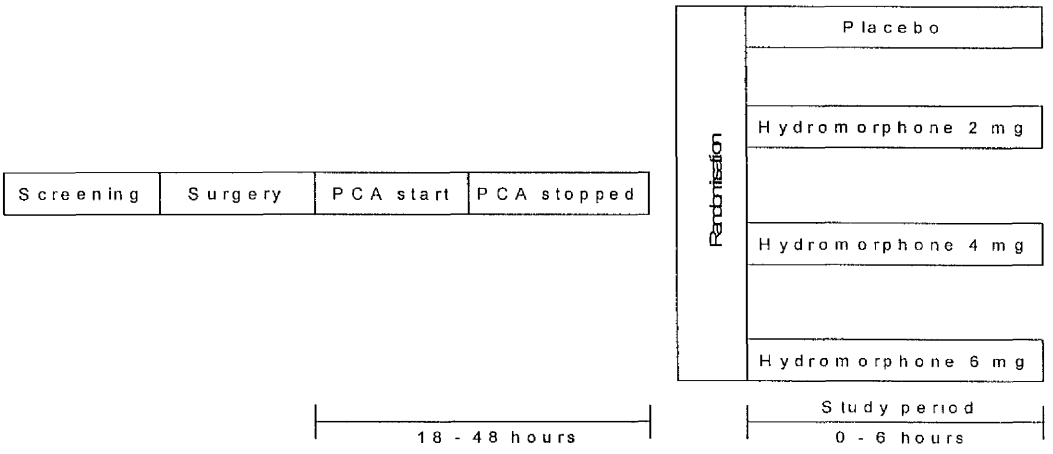
Individuals eligible for entry into this study comprised male or female hospital in-patients, aged 18 years or older, who required post-operative analgesic therapy for pain following primary knee arthroplasty. These patients were to be willing and able to comply with the protocol requirements, and have signed a statement of informed consent before entry.

Individuals not eligible for this study comprised any of the following groups: patients with hypersensitivity to morphine sulphate, hydromorphone hydrochloride or any related compound; patients with a history of drug/alcohol abuse or addiction within a six month period immediately prior to entry; patients who, in the opinion of the investigators, exhibited clinically significant complications (e.g. wound haematoma, active infection or prolonged nausea/vomiting) during or immediately after the knee replacement surgery, or those who had previously undergone major surgery to the affected knee(s) e.g. high tibial osteotomy, open reconstruction of cruciate ligaments, stabilisation of the patella or knee arthroplasty; patients with evidence of clinically significant neurological, haematological, endocrine, cardiovascular, hepatic, renal, gastrointestinal (including nausea and vomiting) or respiratory dysfunction which, in the opinion of the investigator, would interfere with the patients' participation in the study; patients who had received any investigational drug within one month immediately prior to screening for entry into this study; women of child-bearing potential (all had to be given a pregnancy test) who were diagnosed as being pregnant or lactating, and those seeking pregnancy or failing to take adequate contraceptive precautions; individuals previously entered into this study; patients who exhibited significant opioid respiratory depression and sedation due to the use of morphine sulphate in the PCA.

5.2.4.2 Study procedures

A diagram of the study design is given below:

Figure 10. Single-dose acute pain study design



Candidate patients were informed of the nature of the study, and provided written informed consent for participation on admittance to hospital, before the knee surgery. Before and during the surgery, all required medication was to be administered to each participating patient in accordance with the usual hospital practice for such cases. However, the use of an intravenous or subcutaneous patient-controlled analgesia (PCA) system involving morphine sulphate was mandatory for pain control in post-operative recovery. The dose of morphine required by each participating patient was to be titrated appropriately using this system until the pain was well controlled, as defined by observer ratings of pain in the established clinical practice within each individual study centre. In addition to morphine PCA, patients could be administered a single 100 mg dose of diclofenac PR immediately after surgery. Treatment with paracetamol was allowed for the treatment of pyrexia or headache. A minimum 6-hour washout period was required between paracetamol administration and baseline assessment and a minimum 18-hour washout period was required for diclofenac.

Approximately 18-48 hours into the post-operative recovery period, when the pain had been demonstrated to be well controlled for at least two consecutive hours and the resumption of oral intake (fluids and medication) for at least four hours resulted in no clinically significant nausea or vomiting, the use of PCA was to be stopped. Patients who had received nerve blockade were to be assessed to ensure that they had recovered from the effects of the

blockade to establish that their stabilised pain control was entirely due to the morphine PCA.

The $5HT_3$ antagonist ondansetron was to be used to treat post-operative nausea once the patient had taken study medication. Hypnotics, sedatives and tranquillisers were not to be administered to recruited patients within a 6-hour period immediately prior to use of the study medication or during the course of the study period.

As soon as the patients requested further analgesia (taken to be the point at which significant pain reappeared) each individual patient underwent the first (baseline) study assessment of pain intensity (using an 11-point rating scale ranging from 0 = "no pain" to 10 = "pain as bad as you can imagine" for pain at rest and pain on movement). At this stage each patient was to be randomly assigned to one of the four study treatment groups and administered with the single dose of study medication. The pain assessments were to be repeated after 30 minutes, then at hourly intervals throughout the scheduled six-hour study treatment period.

Patients could be withdrawn at any time during the six-hour study treatment period (e.g. because of lack of efficacy or tolerability problems with the study medication). If a patient was withdrawn then the next scheduled pain assessment was to be performed immediately before the withdrawal. If the patient did not withdraw consent all remaining assessments were to be completed at the scheduled times. At the point of withdrawal the patient was to receive the rescue analgesia considered appropriate within the individual hospital (e.g. either re-commencement of morphine therapy with the PCA system or initiation of other parenteral or oral analgesic therapy). The time of re-medication was to be recorded.

5.2.4.3 Study assessments

Table 22 below details the timing of the assessments made in the study.

Table 22. Study schedule

Assessment	Screening[a]	Study Period							
		Hours							
		0	0.5	1	2	3	4	5	6
Informed consent	x								
Eligibility	x								
Demography	x								
Medical history, concomitant disease and medication	x								
Pain at rest		x	x	x	x	x	x	x	x
Pain on movement		x		x	x	x	x	x	x
Sedation		x		x	x	x	x	x	x
Adverse events[b]		x	x	x	x	x	x	x	x

[a] Prior to surgery.

[b] In addition, a follow-up review of adverse events was conducted during the 24 hours immediately after completion of the study period.

Patients' self-reported pain was recorded using the numerical pain scale as shown below. It was derived from the Brief Pain Inventory (Cleeland 1994b).

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Numerical pain rating scores are appropriate for assessing pain (McQuay 1998).

The procedure for assessing pain on movement was defined as flexion of the affected knee required by a patient (in a supine position) to lower the foot by 15 cm from an elevated, fully extended limb position, support for the limb being provided throughout this procedure by the investigator. Patients who were unable to have their foot lowered the full 15 cm because of severe pain, were to provide a score based upon the movement possible.

Active physiotherapy, other than movement of the knee associated with pain assessment, was only performed during the six hour study period provided that 30 minutes had elapsed between physiotherapy and the pain assessments. This provided a recovery time from the effects of physiotherapy to ensure that pain assessments were not affected by the physiotherapy itself. Passive physiotherapy was permitted throughout the study period.

The tolerability for all recruited patients was to be monitored throughout the study period by recording the adverse events experienced. All adverse events were graded for severity according to the following definition:

Severity	Definition
Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities

In addition, sedation was to be assessed at hourly intervals throughout the scheduled study period. Sedation was to be rated with the following 4-point descriptive scale:

0 = Awake, alert, orientated
1 = Dozing intermittently, drowsy or lethargic but aroused by verbal stimulus
2 = Mostly sleeping, difficult to arouse but feasible by physical stimulus
3 = Difficult to waken, little or no response even to physical stimulus

5.2.4.4 Study medication, blinding and randomisation

Patients received a single dose of either hydromorphone 2 mg, 4 mg or 6 mg or placebo, as an instant-release tablet within a capsule (for blinding purposes) orally.

The study medication consisted of brown capsules (size 0) containing 2 mg hydromorphone, 4 mg hydromorphone, 6 mg hydromorphone or matching placebo. The hydromorphone and placebo capsules were identical in appearance, taste and smell. The single dose of medication made available for each patient was packed in a sachet (one capsule per sachet). The study medication was prepared in identical packaging but allocated individual patient numbers. Consequently, both the patient and investigator were unaware of the medication's identity. Sufficient medication supplies were packed and labelled for 400 patients in total (100 patients in each of the four treatment groups).

Allocation of treatment to patients in each of the four study groups was in accordance with a computer-generated randomisation list. At the time of randomisation, each patient was to be given the next available sequential randomisation number. Each study centre was supplied with a sealed envelope for each patient containing details of the administered treatment and dose. An envelope was to be opened only in an emergency, when it was necessary for a patient's treatment to be disclosed. This ensured that the investigator was able to break the code for an individual without unblinding the rest of the study.

5.2.4.5 Data entry and statistical analysis

All data were entered onto Knoll's Oracle Clinical® computer database and then verified by repeat data entry. A 100% audit was carried out of all records relating to site allocation, adverse events, study medication, withdrawal information and the principal measure of efficacy entered in the database against that recorded on the case report forms; a random sample of 15 patients had all their information checked in the same manner. The error rates were 0.35% for adverse events, 0.05% for withdrawal information, 0.55% for site allocation, 0.38% for study medication and 0.01% for the principal measure of efficacy. The error rates were considered to be satisfactory and any discrepancies found were amended before analysis. In addition, manual checks and programmed validation checks were performed.

The statistical methods described in the protocol were expanded to produce a detailed statistical plan. This was discussed and agreed before the blind was broken and data made available for analysis.

All calculations were performed using SAS (SAS Institute Inc 1990). Williams' test (1972) was performed using a validated in-house SAS program. All statistical tests performed were two-tailed, and the null hypothesis was at all times that the treatment groups (each dose of active medication compared to placebo) were equal. Statistical significance was determined by reference to the 5% level, unless otherwise stated. Also, 95% confidence intervals are presented for the difference between each dose and placebo. These confidence intervals were always constructed to correspond with the p-value from Williams' test (i.e. if the p-value indicated statistical significance at the 5% level then the confidence intervals were not to contain zero and vice versa).

The "full analysis" set (referred to as the intent-to-treat efficacy analysis in the protocol) included all patients who took study medication with at least one assessment performed within the post-baseline phase. Patients who withdrew from the study and/or were given rescue medication had their last observed value for the relevant efficacy variable(s) carried forward for all time periods subsequent to withdrawal or re-medication. In all the above analyses, any patients with treatment administration errors were analysed according to the treatment actually taken.

Due to the expected relatively small number of major protocol violations, no per-protocol analysis was performed. All relevant protocol deviations were assessed under blind conditions. All patients taking at least one dose of study medication were included in the analysis of safety.

The treatment groups were assessed for comparability with respect to baseline information, in particular the total dose of morphine administered as PCA prior to stopping and the time from stopping PCA to study medication dispensed. Any clinically significant difference was accounted for in the subsequent analysis.

The principal measure of efficacy was the SPID for the seven post-baseline assessments for pain at rest. This together with the following variables was analysed by analysis of covariance (Armitage 1987, p282-95) with factors for treatment and country with the baseline pain score as a covariate:

- the SPID for the six post-baseline assessments for pain on movement
- the changes from baseline at each of the post-baseline assessments for pain at rest and pain on movement

In each case, Williams' test using estimates from the analysis of covariance (ANCOVA) was used to compare each dose of active medication with placebo and hence establish the minimum effective dose. For the principal measure of efficacy only, an additional analysis, including a factor for the treatment-by-country interaction was performed. If this interaction was significant at the 10% level, the source of the interaction and its impact on the results were to have been assessed.

As there was an imbalance between the treatment groups for the time from stopping PCA to the time study medication was dispensed, it was decided for the principal measure of

efficacy only, that an additional analysis of covariance would be performed. This included an additional factor having five levels for the elapsed time from stopping PCA to the dispensing of study medication, these levels were 0-60, 61-120, 121-180, 181-240, >240 minutes.

After codebreak it was decided it was appropriate to perform an analysis which gave some indication of the duration of action of the respective hydromorphone doses and placebo. Therefore, the time to pain at rest returning to the baseline value was analysed using the logrank test with p-values for pairwise comparisons against placebo adjusted by Sidak. To allow for the time to drug effect, assessments recorded less than 60 minutes after dosing were disregarded from the calculation. Patients who withdrew/re-medicated before pain at rest returned to baseline value had their values censored at the time of re-medication/withdrawal. Patients who completed the study without returning to their baseline value had their values censored at the time of their six-hour assessment.

For all the above analyses, patients who withdrew from the study and/or were given rescue medication had their last observed value carried forward for all time periods subsequent to withdrawal or re-medication.

The severity of a recurrent adverse event was taken to be the most severe of the occurrences and the relationship to therapy as the most probable. In counting the number of events reported, a continuous event, i.e. reported more than once and which did not cease, was counted only once; non-continuous adverse events reported several times by the same patient were counted as multiple events. Events present at baseline that did not worsen in severity were not included.

The difference between the treatment groups in the proportion of patients with adverse events was compared using the chi-square test (Armitage 1987, p205-9). Data on sedation were tabulated by treatment group with 95% confidence intervals for the pairwise differences with placebo.

Initially the study was analysed in a blind fashion, treatment groups were known only as A, B, C and D. Normality assumptions were tested by an examination of the residual plots and the Shapiro-Wilk test (1965) of normality; homogeneity of variance was tested using

Levene's test (Milliken 1984) about the median. Depending on the degree of departure from these assumptions, an alternative nonparametric approach would have been used instead. Only when these decisions were made and documented was the full key to the randomisation released.

The principal measure of efficacy was the SPID for the seven post-baseline assessments of pain at rest. The sample size was estimated to be 50 patients per treatment group. This figure allowed a detection of a treatment difference of 7.0 between any dose of hydromorphone and placebo – assuming a variability (sd) of 11.0 (estimated using data from a previous study), 90% power, a 5% significance level and a Williams' test. The actual variability estimated from the root mean square error (MSE) from the analysis of covariance was 12.4.

5.2.5 Results

5.2.5.1 Efficacy

A total of 281 patients were screened for entry into the study between 5 January 1999 and 31 May 1999, of which 205 actually took study medication. Of the 205 patients randomised, 129 completed the study. Table 23 below gives the number of patients entering and completing the double-blind phase by centre within each country:

Table 23. Summary of number of patients completing and entering the double-blind phase by centre within each country

Country/ centre number	Treatment group				Overall
	Hyd. 2 mg	Hyd. 4 mg	Hyd 6 mg	Placebo	
France	16/17 (94%)	16/17 (94%)	15/18 (83%)	14/17 (82%)	61/69 (88%)
Netherlands	9/18 (50%)	8/17 (47%)	6/14 (43%)	9/19 (47%)	32/68 (47%)
United Kingdom	8/16 (50%)	8/15 (53%)	11/19 (58%)	9/18 (50%)	36/68 (53%)

Withdrawals and reason for withdrawal are summarised in Table 24 below.

Table 24 Summary of patient withdrawals during the double-blind phase

Reason for withdrawal	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Placebo
Total number of patients	51	49	51	54
Adverse event				
0-3 hours	-	2	-	1
> 3-6 hours	1	1	-	-
Overall	1	3	-	1
Lack of efficacy				
0-3 hours	14	13	14	18
>3-6 hours	1	1	5	3
Overall	15	14	19	21
Protocol violation				
0-3 hours	1	-	-	-
>3-6 hours	-	-	-	-
Overall	1	-	-	-
Withdrawal of consent				
0-3 hours	1	-	-	-
>3-6 hours	-	-	-	-
Overall	1	-	-	-
Total withdrawn	18 (35%)	17 (35%)	19 (37%)	22 (41%)

A summary of protocol deviations for all patients randomised is provided in Table 25 below.

Table 25. Protocol deviations

Deviation[a]	Treatment group				Overall
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo	
Major deviations					
Took inadmissible analgesics	4	2	4	1	11
Less than 18 hours between rectal diclofenac dose and ceasing PCA	4	1	-	2	7
Inadmissible duration between surgery and taking study medication	-	-	1	-	1
Previous knee replacement surgery to affected knee	-	-	-	2	2
Previous high tibial osteotomy to affected knee	1	-	-	1	2
Previous open reconstruction of cruciate ligaments of affected knee	-	-	-	1	1
Number of patients with major deviations	9	3	5	7	24
Minor deviations					
Took anti-emetics less than eight hours prior to study medication dosing	2	2	-	-	4
Took hypnotics during the study	-	1	2	1	4
Took opioids during the study	1	1	1	1	4
Physiotherapy between operation and taking study medication	1	-	-	-	1
No written consent at screening	-	1	-	-	1
Number of patients with minor deviations	4	5	3	2	14
Number of patients with a deviation	12	7	7	7	33

[a] Not mutually exclusive

A total of 205 patients entered the double-blind phase of the study, all of whom provided at least one post-baseline efficacy assessment. Patient number 738 (placebo group) provided no baseline data for pain at rest, therefore 204 patients were included in the analysis of the principal measure of efficacy, the SPID of pain at rest. For the analysis of pain on movement, 199 patients were included with six patients providing no baseline data.

The treatment groups were relatively well balanced with respect to all demographic variables tabulated, as summarised in Table 26 below:

Table 26. Summary of entry profile for all patients randomised

Variable	Treatment group				Overall
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo	
n	51	49	51	54	205
Mean age ± sd (yr)	68.1 ± 9.1	68.4 ± 11.1	67.5 ± 10.0	67.1 ± 9.6	67.8 ± 9.9
Female	30 (59%)	34 (69%)	28 (55%)	34 (63%)	126 (61%)
Caucasian	50 (98%)	49 (100%)	51 (100%)	52 (96%)	202 (99%)
Mean height ± sd (cm)	165.9 ± 7.6	166.7 ± 9.2	167.1 ± 8.3	165.6 ± 8.9	166.3 ± 8.5
Mean weight ± sd (kg)	78.1 ± 14.8	82.6 ± 16.4	80.9 ± 12.2	79.8 ± 16.5	80.3 ± 15.1

There was a statistically significant imbalance between treatment groups for the time from stopping PCA to the time study medication was dispensed. The percentage of patients in each group with an elapsed time of ≤120 minutes was 41%, 47%, 71% and 65% for the hydromorphone 2 mg, 4 mg and 6 mg and the placebo groups, respectively. One patient in the hydromorphone 6-mg group had 4565 minutes (i.e. just over three days) between stopping PCA and the dispensing of study medication. A total of 162 (79%) of patients had regional anaesthetic procedures. There were imbalances between countries with respect to total duration of PCA use and the corresponding time from the operation to the dispensation of study medication. Patients in the UK, in general, received PCA morphine over a longer time period compared to patients in the other two countries. The consumption of morphine in mg/hour was broadly similar across the countries, with the lower values in the UK being possibly related to diminished morphine use as time from surgery increased. In addition, 41 patients received non-PCA morphine during the post-operative period. Table 27 below summarises these imbalances.

Table 27. Summary of selected PCA variables by country

Variable	Country			Overall
	France	Netherlands	UK	
n	69	68	68	205
Median morphine dose administered as PCA (mg)	37.2	39.5	54.5	40.0
Median amount of morphine sulphate administered as PCA per hour	1.81	1.80	1.57	1.77
Median total duration of PCA (h)	20.3	21.0	39.0	21.3
Median time from operation to study medication dispensed (h)	23.3	23.6	44.4	24.3

Doses in milligrams were treated as equivalent, whether they were administered intravenously or subcutaneously, since they are assumed to be equipotent (Twycross 1998).

Table 28 below presents summary statistics of the total amount of morphine administered (including non-PCA) tabulated by whether the single 100-mg dose of diclofenac was given peri-operatively or in early postoperative management. Morphine consumption was higher in patients who did not receive the rectal dose.

Table 28. Total morphine administered by diclofenac use

	Morphine consumption (mg)				
Diclofenac used	n	Mean	Median	sd	Range
Yes	32	44.4	38.5	25.7	12, 142
No	173	52.0	45.0	32.6	9, 232
Overall	205	50.8	44.0	31.7	9, 232

Predictably, the most commonly reported previous condition was localised osteoarthritis, reported by 62 patients (30%). Of the 144 (70%) patients that had concomitant musculoskeletal, connective tissue and bone disorders, 72 (50%) had osteoarthritis, 51 (35%) had localised osteoarthritis and 12 (8%) had rheumatoid arthritis.

A total of 183 (89%) patients reported previous medications in the seven days prior to entry including 137 (67%) patients who received anaesthetics, 75 (37%) patients who used analgesics, 68 (33%) patients who used psycholeptics (see below) and 57 (28%) patients who used anti-inflammatory and anti-rheumatic products. One-hundred-and-ninety-five (95%) patients were receiving concomitant medications prior to the operation including 113 (55%) who were taking antithrombotic agents and 108 (53%) who were taking antibacterials for systemic use.

A total of 158 (77%) patients commenced medications other than morphine sulphate between the operation and randomisation. Table 29 below summarises anti-emetics commencing between the operation and randomisation:

Table 29 Summary of anti-emetics commencing between the operation and randomisation

	Treatment group				
Anti-emetic[a]	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo	Overall
Total number of patients	51	49	51	54	205
Number of patients commencing anti-emetics	21 (41%)	17 (35%)	16 (31%)	17 (31%)	71 (35%)
Cyclizine	3	1	5	-	9
Haloperidol	-	-	-	1	1
Metoclopramide	3	4	1	2	10
Ondansetron hydrochloride	18	13	13	15	59

[a] Not mutually exclusive

Forty-one (20%) patients commenced medications during the double-blind phase including 20 (10%) patients who took antibacterials for systemic use. A total of ten patients commenced using ondansetron hydrochloride during the double-blind phase, one in hydromorphone 2 mg group, three in the hydromorphone 4 mg group, two in the hydromorphone 6 mg group and four in the placebo group.

For SPID for pain at rest, hydromorphone 4 mg and 6 mg were significantly more effective in reducing pain at rest compared with placebo (p=0.03 for both comparisons). There was no statistically significant difference between hydromorphone 2mg and placebo (p=0.24). The adjusted means for the SPID were -2.3 for hydromorphone 2 mg, -5.2 for hydromorphone 4 mg, -4.4 for hydromorphone 6 mg and 0.6 for placebo. Table 30 below summarises the data:

Table 30. Analysis of covariance for SPID for pain at rest

SPID for pain at rest[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Placebo
n	51	49	51	53
Mean±sd	-2.7±14.0	-5.2±13.7	-4.3±13.7	0.8±14.1
Range	-35,26	-47,22	-33,33	-33,36
Adjusted mean[b]	-2.3	-5.2	-4.4	0.6
Difference in adjusted means relative to placebo[c]	-2.9	-5.7	-5.0	
se (of difference)	2.4	2.4	2.4	
Williams' test (LSD = 4.97)				
P-value (versus placebo)	0.24	0.03	0.03	
95% CI for difference[d]	-7.6,1.9	-11.2,-0.001[e]	-11.2,-0.001[e]	

[a] A negative value denotes an improvement from baseline
[b] Adjusted for baseline and country
[c] A negative difference favours hydromorphone
[d] Not symmetric around the differences in the adjusted means due to the assumption of a monotonic trend
[e] As Williams' test was statistically significant, upper bound of confidence interval was made to be consistent with the significance of the test i.e. it did not contain zero

In the ANCOVA the terms for country and treatment group-by-country interaction were not statistically significant (p=0.054 and p=0.61, respectively), the latter implying that treatment differences were comparable across countries. Table 31 below summarises mean SPID pain at rest scores by treatment and country:

Table 31. Mean (n) SPID for pain at rest by treatment group and country

Variable	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo
Overall	-2.7 (51)	-5.2 (49)	-4.3 (51)	0.8 (53)
France	-2.7 (17)	-3.2 (17)	0.3 (18)	1.9 (17)
Netherlands	-1.6 (18)	-7.5 (17)	-7.5 (14)	1.9 (18)
United Kingdom	-4.1 (16)	-4.7 (15)	-6.3 (19)	-1.4 (18)

As there was an imbalance between treatments in the time from stopping PCA to the time study medication was dispensed, an additional analysis was performed with this as a five-level factor in the ANCOVA. The results obtained were similar to the main analysis.

For the analyses at individual time-points for pain at rest, the hydromorphone 6 mg versus placebo comparison was statistically significant at hour 1 (p=0.02), similarly at hour 2 (p=0.013). At hour 3, the hydromorphone 4 mg versus placebo and hydromorphone 6 mg versus placebo comparisons were statistically significant (p=0.008 in each case). At 4, 5 and

6 hours, none of the pairwise comparisons were statistically significant. A summary is given below in Figure 11 for the mean pain at rest and Table 32 for the adjusted mean changes from baseline in pain at rest at each follow-up assessment. The mean decreases in pain in the hydromorphone groups were largest over the first three hours.

Figure 11. Mean pain at rest (carry forward data)

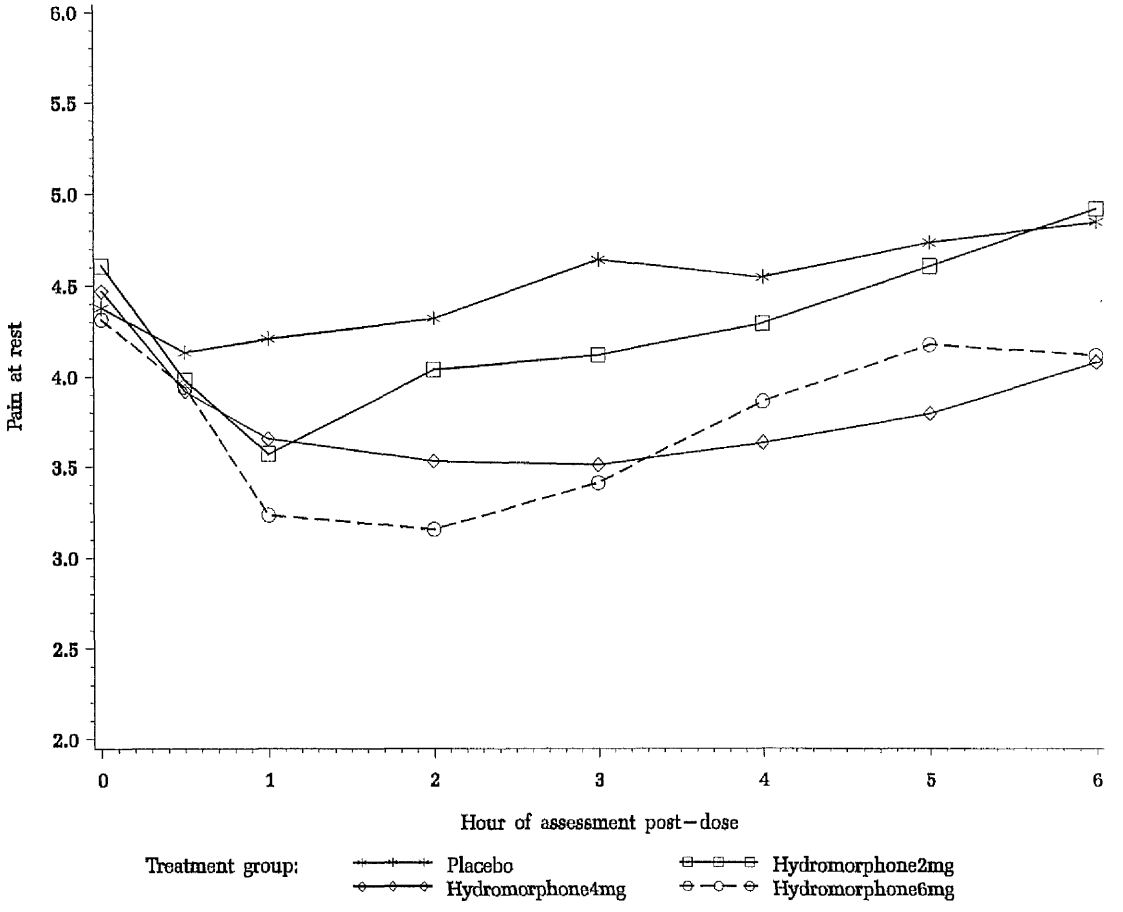


Table 32. Adjusted mean changes[a] from baseline in pain at rest at each follow-up assessment (carryforward data)

Hour	Treatment group			
	Hyd. 2 mg (n=51)	Hyd. 4 mg (n=49)	Hyd. 6 mg (n=51)	Placebo (n=53)
0.5	-0.6	-0.6	-0.4	-0.3
1	-1.0	-0.8	-1.1*	-0.2
2	-0.5	-0.9	-1.2*	-0.1
3	-0.4	-1.0**	-0.9**	0.2
4	-0.2	-0.8	-0.5	0.1
5	0.1	-0.7	-0.2	0.3
6	0.4	-0.4	-0.2	0.4

[a] Adjusted for baseline and country
* p<0.05 versus placebo
** p<0.01 versus placebo

For SPID for pain on movement, hydromorphone 4 mg and 6 mg were significantly more effective in reducing pain on movement than placebo (p=0.04). There was no statistically

significant difference between hydromorphone 2 mg and placebo (p=0.60). The adjusted means for SPID were -1.3 for hydromorphone 2 mg, -5.6 for hydromorphone 4 mg, -3.9 for hydromorphone 6 mg and -0.2 for placebo. Figure 12 and Table 33 below summarises the data:

Figure 12. Mean pain on movement (carryforward data)

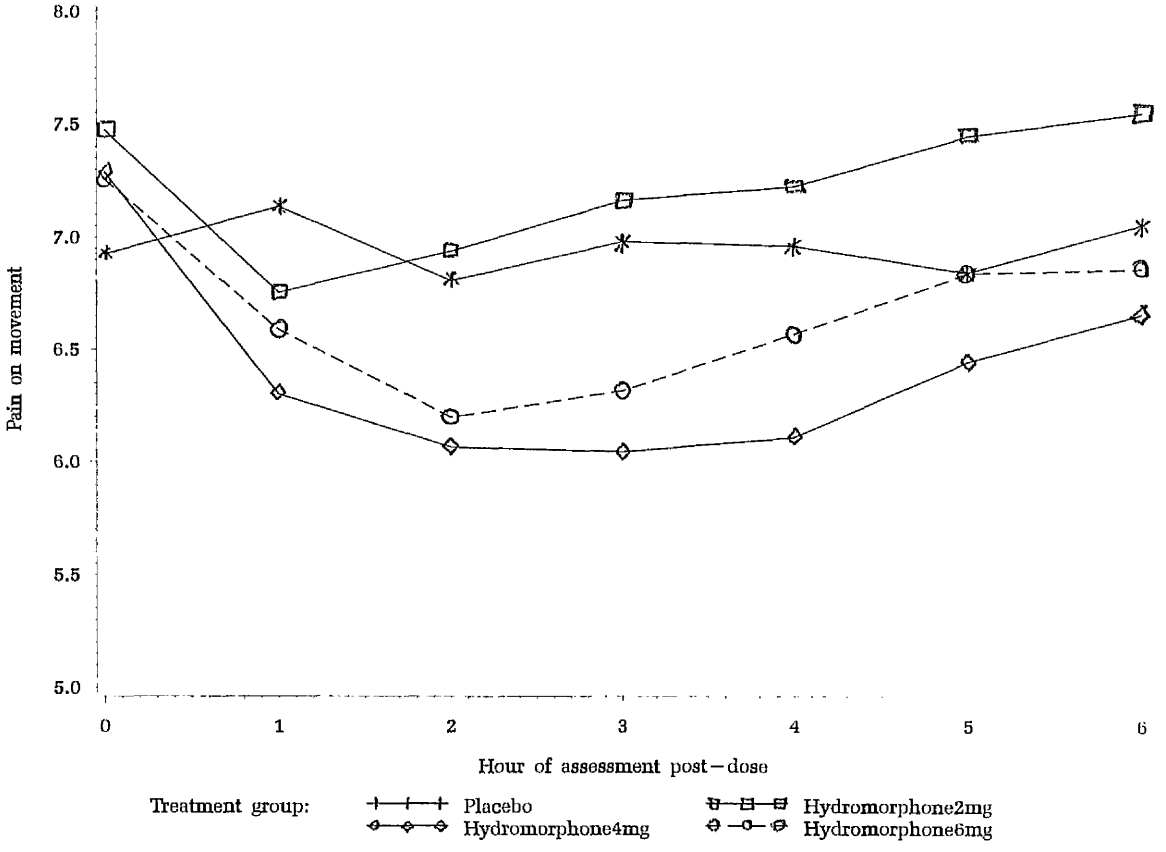


Table 33. Analysis of covariance for SPID for pain on movement

SPID for pain on movement[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Placebo
n	49	47	51	52
Mean ± sd	-1.9 ± 11.1	-5.7 ± 12.7	-4.2 ± 12.1	0.5 ± 9.5
Range	-26,25	-32,27	-30,34	-18,27
Adjusted mean[b]	-1.3	-5.6	-3.9	-0.2
Difference in adjusted means relative to placebo[c]	-1.1	-5.4	-3.7	
se (of difference)	2.1	2.1	2.1	
Williams' test (LSD = 4.31)				
P-value (versus placebo)	0.60	0.04	0.04	
95% CI for difference[d]	-5.3,3.0	-9.5,-0.001[e]	-9.5,-0.001[e]	

[a] A negative value denotes an improvement from baseline

[b] Adjusted for baseline and country

[c] A negative difference favours hydromorphone

[d] Not symmetric around the differences in the adjusted means due to the assumption of a monotonic trend

[e] As Williams' test was statistically significant, upper bound of confidence interval was made to be consistent with the significance of the test i.e. it did not contain zero

For the analyses at individual time-points for pain on movement, the comparisons of all hydromorphone doses versus placebo were statistically significant at hour 1 (p=0.012 for hydromorphone 2 mg, p=0.006 for hydromorphone 4 mg and p=0.005 for hydromorphone 6 mg). At hours 2 and 3 the hydromorphone 4 mg and 6 mg comparisons versus placebo were statistically significant (p=0.04 at hour 2 and p=0.02 at hour 3 for hydromorphone 4 mg and 6 mg). At 4, 5 and 6 hours, none of the pairwise comparisons were statistically significant. A summary is given in Table 34 below for the adjusted mean changes from baseline in pain on movement at each follow-up assessment:

Table 34. Adjusted mean changes[a] from baseline in pain on movement at each follow-up (carryforward data)

Hour	Treatment group			
	Hyd. 2 mg (n=49)	Hyd. 4 mg (n=47)	Hyd. 6 mg (n=51)	Placebo (n=52)
1	-0.7*	-0.9**	-0.6**	0.2
2	-0.5	-1.2*	-1.0*	-0.2
3	-0.2	-1.2*	-0.9*	-0.0
4	-0.2	-1.1	-0.6	-0.0
5	0.1	-0.8	-0.4	-0.2
6	0.2	-0.6	-0.3	0.0

[a] Adjusted for baseline and country
* p<0.05 versus placebo
** p<0.01 versus placebo

The proportion of patients reporting the use of rescue analgesia was higher in the placebo group (39%) compared to the three hydromorphone groups (31% for 2 mg, 33% for 4 mg and 33% for 6 mg). The most commonly reported rescue medication was morphine, which was taken by 44 patients during the double-blind phase.

For the analysis of the time to pain at rest returning to the baseline value, the overall treatment group comparison was not statistically significant (p=0.07), although the pairwise comparison between hydromorphone 6mg and placebo was significant (p=0.013). The Kaplan-Meier estimates for time for pain at rest returning to baseline value were 165.4, 191.6, 209.5 and 109.7 minutes for the hydromorphone 2, 4 and 6mg groups and the placebo groups respectively. The number of patients reporting pain values returning to the original baseline was over 60% in all four treatment groups, with highest incidence rate in the placebo group (77%) and the lowest in the hydromorphone 6mg group (63%; Table 35). The Kaplan-Meier plot for time to first report of pain at rest returning to the original baseline is presented in Figure 13.

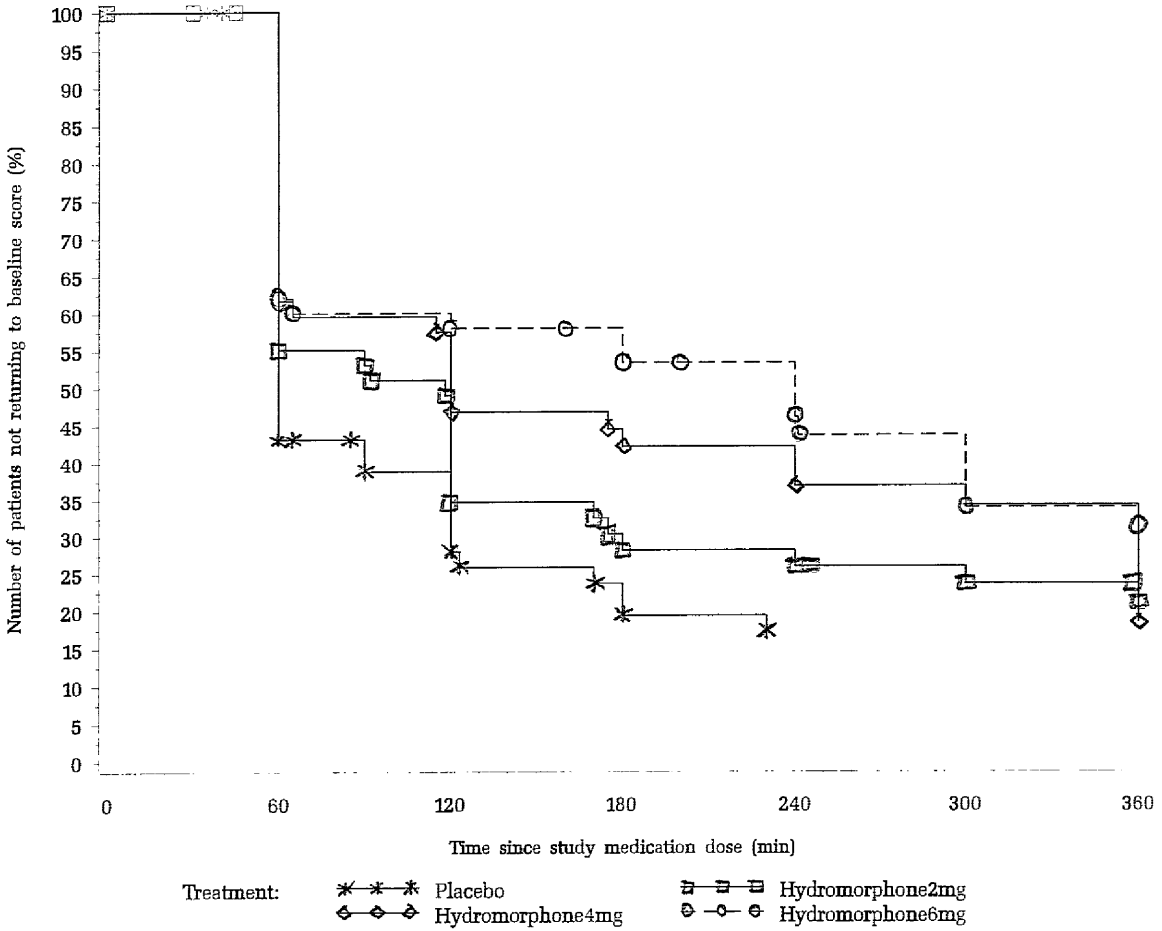
Table 35. Time to first report of pain at rest returning to baseline value

Time to first report of pain at rest returning to baseline value [a] (min)	Treatment group			
	Hydromorphone 2mg	Hydromorphone 4mg	Hydromorphone 6mg	Placebo
Total number of patients	51	49	51	53
Number of patients reporting	39 (76%)	36 (73%)	32 (63%)	41 (77%)
Comparisons (logrank test)	χ^2	df		p
Overall	7.15	3		0.07
Hydromorphone 2mg versus placebo	0.76	1		0.38
Hydromorphone 4mg versus placebo	2.18	1		0.14
Hydromorphone 6mg versus placebo	6.23	1		0.013
60	22	18	19	29
61-120	10	7	2	7
121-180	3	2	2	4
181-240	1	2	3	1
>240	3	7	6	-
Mean[b]	165.4	191.6	209.5	109.7
se	19.4	19.9	19.3	9.7

a Time calculated from time of dispensing of medication. Assessments recorded less than 60 minutes after dosing are disregarded in the calculation as were assessments made after re-medication/withdrawal

b Kaplan-Meier estimate. Patients whose pain did not return to the baseline value who did not re-medicate/withdraw within the first six hours had their time censored at the time of their hour 6 assessment

Figure 13 Kaplan-Meier estimates for time to pain at rest returning to the baseline value



Hydromorphone 4 mg and 6 mg were therefore clinically and statistically significantly more efficacious than placebo in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery.

5.2.5.2 Safety

Fifty-one, 49, 51 and 54 patients received single doses of immediate-release hydromorphone 2 mg, 4 mg and 6 mg and placebo, respectively.

The number of patients reporting an event during the double-blind phase and the number of events in each treatment group are summarised in Table 36 below:

Table 36 Summary of adverse events reported during the double-blind phase

	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo
Total number of patients	51	49	51	54
Number of patients reporting an adverse event	11 (22%)	15 (31%)	17 (33%)	15 (28%)
Number of events reported	17	20	19	21

The severity and relationship to therapy of adverse events reported during the double-blind phase are presented in Table 37 below:

Table 37 Summary of severity and relationship to therapy during the double-blind phase

		No of reports (%)			
		Treatment group			
		Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo
Severity	Mild	13 (76%)	11 (55%)	15 (79%)	15 (71%)
	Moderate	4 (24%)	7 (35%)	4 (21%)	5 (24%)
	Severe	-	2 (10%)	-	1 (5%)
Relationship to therapy	Probable	3 (18%)	4 (20%)	8 (42%)	7 (33%)
	Possible	5 (29%)	6 (30%)	5 (26%)	3 (14%)
	Unlikely	4 (24%)	6 (30%)	4 (21%)	5 (24%)
	None	5 (29%)	4 (20%)	2 (11%)	6 (29%)

The most commonly reported events (i.e. reported by more than 5% of patients in any treatment group) are summarised in Table 38 below:

Table 38 Summary of adverse events reported by >5% of patients in any treatment group during double-blind phase

MedDRA* preferred term	Number of patients reporting			
	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Placebo
NAUSEA	1 (2%)	3 (6%)	3 (6%)	5 (9%)
VOMITING	1 (2%)	5 (10%)	2 (4%)	2 (4%)
PYREXIA	1 (2%)	3 (6%)	2 (4%)	2 (4%)
HAEMATOMA	-	-	-	3 (6%)

* Medical Dictionary of Regulatory Activities

Generally, the reports of nausea and vomiting were assessed by the investigator as being probably or possibly related to treatment, whilst reports of pyrexia were assessed as having an unlikely or no relationship to treatment.

Table 39 below lists the number of patients who had the commonly reported side effects associated with morphine (Moulin 1996) ongoing during the double-blind phase. This table includes patients who had ongoing adverse events at the time of randomisation which were not attributable to treatment.

Table 39 Summary of ongoing adverse events commonly reported with morphine during the double-blind phase (Moulin et al, 1996)

MedDRA preferred term	Number of patients reporting			
	Treatment group			
	Hyd. 2 mg (n=51)	Hyd. 4 mg (n=49)	Hyd. 6 mg (n=51)	Placebo (n=54)
ABDOMINAL PAIN	1 (2%)	-	-	1 (2%)
ABDOMINAL PAIN UPPER	1 (2%)	-	-	-
CONSTIPATION	-	1 (2%)	-	1 (2%)
DIARRHEA	-	-	-	1 (2%)
DRY MOUTH	1 (2%)	-	1 (2%)	-
NAUSEA	2 (4%)	4 (8%)	5 (10%)	5 (9%)
VOMITING	1 (2%)	5 (10%)	3 (6%)	2 (2%)
DIZZINESS (EXC VERTIGO)	-	-	2 (4%)	-
SEDATION	-	-	-	1 (2%)
SOMNOLENCE	-	-	1 (2%)	-
CONFUSION	-	1 (2%)	-	-
SLEEPING DISORDER	1 (2%)	1 (2%)	-	2 (2%)
PRURITUS	-	1 (2%)	1 (2%)	-
Number of patients reporting any of the above	7 (14%)	13 (27%)	11 (22%)	12 (22%)

Five patients withdrew due to adverse events during the double-blind phase, one in the hydromorphone 2-mg group, three in the hydromorphone 4-mg group and one in the placebo group. Patient number 667 (hydromorphone 2 mg) withdrew from the study because of pain, which was reported as mild and probably related to study medication. He

was given symptomatic therapy and the outcome was reported as resolved. Patient 519 (hydromorphone 4 mg) withdrew due to a headache of moderate severity, which was reported as being not related to study therapy. She was given symptomatic therapy for the headache, which resolved. Patient 529 (hydromorphone 4 mg) withdrew due to moderate pyrexia, which was not related to study therapy. He was given symptomatic therapy and the event resolved. Patient 837 (hydromorphone 4 mg) withdrew from the study because of mild anxiety possibly related to study medication. No action was taken and the event resolved. Patient number 581 (placebo) withdrew due to severe nausea probably related to study therapy. She was given symptomatic therapy and the nausea resolved.

The difference between treatment groups in the proportion of patients reporting adverse events during the double-blind phase was not statistically significant ($p=0.59$). There were no deaths during the study and no serious adverse events.

The percentage of patients being awake, alert and orientated was, in general, lower in the placebo group at each hourly assessment (Table 40). Scores of 1 in the sedation scale (dozing intermittently, drowsy or lethargic but roused by physical stimulus) were equal at baseline, but more prevalent in active treatment groups in the measures made after dosing. Generally, the 95% confidence intervals for these measures did not suggest a statistically significant finding. Within the treatment groups, there did not appear to be a relationship with dose level. The five individual reports of scores of 2 were equally distributed between the hydromorphone and placebo groups.

Table 40. Level of sedation at each assessment (observed data)

Time (hours)	Treatment group	Level of sedation[a] n	0	1	2	3	% graded as 0	Difference relative to placebo	95% CI for difference
Baseline	Hydromorphone 2mg	51	45	6	-	-	88	-3	-14,9
	Hydromorphone 4mg	49	41	8	-	-	84	-7	-20,6
	Hydromorphone 6mg	51	48	3	-	-	94	3	-7,13
	Placebo	54	49	5	-	-	91		
1	Hydromorphone 2mg	49	40	9	-	-	82	10	-6,26
	Hydromorphone 4mg	48	35	13	-	-	73	1	-16,19
	Hydromorphone 6mg	50	38	11	1	-	76	4	-13,21
	Placebo	53	38	15	-	-	72		
2	Hydromorphone 2mg	47	38	9	-	-	81	11	-6,29
	Hydromorphone 4mg	46	31	15	-	-	67	-2	-21,17
	Hydromorphone 6mg	49	35	14	-	-	71	2	-16,20
	Placebo	49	34	15	-	-	69		
3	Hydromorphone 2mg	44	38	6	-	-	86	18	1,36
	Hydromorphone 4mg	43	31	12	-	-	72	4	-16,23
	Hydromorphone 6mg	46	38	8	-	-	83	14	-4,32
	Placebo	41	28	12	1	-	68		
4	Hydromorphone 2mg	42	33	9	-	-	79	12	-7,31
	Hydromorphone 4mg	40	31	8	1	-	78	11	-9,30
	Hydromorphone 6mg	41	35	6	-	-	85	19	0,37
	Placebo	39	26	12	1	-	67		
5	Hydromorphone 2mg	40	30	10	-	-	75	8	-12,29
	Hydromorphone 4mg	37	30	7	-	-	81	14	-5,34
	Hydromorphone 6mg	36	31	5	-	-	86	19	0,39
	Placebo	36	24	11	1	-	67		
6	Hydromorphone 2mg	41	36	5	-	-	88	4	-11,20
	Hydromorphone 4mg	37	32	5	-	-	86	3	-13,20
	Hydromorphone 6mg	34	28	6	-	-	82	-1	-19,17
	Placebo	36	30	6	-	-	83		

a Measured on a 4-point scale (0 = awake, alert, orientated; 1 = dozing intermittently, drowsy or lethargic but aroused by physical stimulus; 2 = mostly sleeping, difficult to arouse but feasible by physical stimulus; 3 = difficult to waken, little or no response even to physical stimulus)

Therefore, it would appear that in this setting, the tolerability of the three hydromorphone doses was comparable to placebo.

5.2.6 Discussion

This study collected standardised data in a complex and varied setting. Treatment for postoperative pain varies between practitioners in the same hospital, so differences in practice are inevitably an issue in a study conducted across multiple centres in three countries. The need to control variables in the study conflicts with the ability to recruit sufficient numbers of centres and patients in order to be able to conduct the study in a practicable manner.

The controls in this study began once the patient left the operating theatre. Morphine PCA (subcutaneous or intravenous) was to be the principal analgesic, with an optional single dose of 100 mg of rectal diclofenac. Paracetamol and NSAID treatments have become extremely well established in the treatment of post-operative patients (Kehlet 1999), so excluding them would have caused severe difficulties in the management of the study. For the purpose of managing pyrexia and headache during the PCA period, paracetamol was permitted provided that at least 6 hours elapsed between administration and the study baseline assessment. This was to ensure that the analgesia assessed at baseline was attributable only to morphine PCA. Active physiotherapy was to precede pain assessments by at least 30 minutes, thus enabling an assessment of background pain, rather than acute pain attributable to the physiotherapy itself.

The elements that were not controlled by the study were the anaesthetic procedure itself and the use of a single rectal dose of 100 mg diclofenac peri-operatively for early post-operative pain management in some study centres. The variability in anaesthetic technique resulted in some patients receiving regional anaesthetic procedures which had long durations of action. This resulted in the use of morphine PCA being superimposed on persisting effects from regional anaesthesia. However, the effects of these long-duration treatements should have resolved by the time of randomisation (a minimum of 18-hours post surgery).

Hydromorphone 4 mg and 6 mg were significantly more effective than placebo in the relief of post-operative pain. Mean SPID values for pain at rest, the principal efficacy measure, were –5.2 and –4.4 for hydromorphone 4 and 6 mg, respectively ($p=0.03$ compared with placebo). These results are comparable with other placebo controlled study of opioids in postoperative pain, although these studies used a 4-point categorical pain score, rather than the 11-point numerical one used here (Baird 1980, Sunshine 1996).

The study precision was adequate to meet the study objectives, the LSD for the principal efficacy measure was 4.97 compared to the detectable difference of 7.0 quoted in the protocol, despite the variability (S.D.) being slightly larger at 12.4 than predicted (11.0). All treatment differences were less than 7.0, however this value was never deemed to be the smallest clinically relevant difference.

Results were similar for the analyses of pain on movement: mean values for SPID were –5.6 and –3.9 for hydromorphone 4 mg and 6 mg, respectively (p=0.04 compared with placebo). Both doses were also superior to placebo in the analysis of the AUC for pain on movement (p=0.03). Again, the decreases in pain on movement were greatest during the first three hours post-treatment.

A total of 76 (37%) patients withdrew from the study. Of these patients, the proportion using rescue medication was highest in the placebo group (39%). Completion rates in the respective countries varied (88% in France, 53% in the UK and 47% in the Netherlands). Within countries, there were marked differences between centres in respect to the percentage of patients completing the 6-hour study period. Within each centre, however, the completion rate did not vary greatly between the study treatments. This suggests that the variability was due to investigator differences, rather than treatment-related factors. Seventy of the patients who withdrew from the study used rescue medication. Morphine was the most commonly used rescue medication, being administered in 44 (63%) patients. The proportion of patients receiving morphine as rescue medication was similar across the dose groups. The dropout rate meant that values for the efficacy endpoint (pain at rest) had to be imputed for the times of measurement after which an individual patient withdrew from the study. A last-observation-carried-forward method was used for this, as recommended by the Food and Drug Administration of the USA (FDA 1995).

A total of 148 patients (72%) reported pain at rest which returned to the original baseline value. The highest proportion occurred in the placebo group (77%), whilst the lowest proportion was in the hydromorphone 6 mg group (63%). The Kaplan-Meier estimates for time for pain at rest returning to baseline value were 165.4, 191.6, 209.5 and 109.7 minutes for the hydromorphone 2, 4 and 6 mg groups and the placebo group, respectively. The comparison between hydromorphone 6 mg and placebo was statistically significant, although the comparison between 2 mg and placebo and 4 mg and placebo were not statistically significant.

The absolute mean change measured in the 11-point numerical rating scale used was relatively small, being somewhat less than one point. The study was sufficiently precise to be able to attach a statistical significance to this difference, but the clinical significance of this degree of change is a separate issue. This amount of change would probably not be

regarded as significant in a clinical setting, but there are several factors in the study setting which constrain the outcome. One of these is the variability of patients' response to opioid analgesia (Ogilvy 1994) and the inability to allow for this variability in the study setting where dose level and dosing regimen is fixed. A second factor is the use of hydromorphone as a monotherapy in the study setting. In the clinical setting, combinations of opioids and non-opioid agents would be used (Ogilvy 1994, Kehlet 1999). Another factor in the study setting is the expectation of the patient regarding the degree of analgesia. Although the study was double-blind, the process of informed consent ensured that patients were aware that they might receive a placebo dose and further, that they had the opportunity to leave the study at any time and receive alternative analgesia, hence the large numbers of patients withdrawing due to lack of efficacy. These factors combined to create a poor expectation of pain relief on the patients' part and patients' expectations can affect the degree of analgesia that they experience (Pollo 2001, Rowbotham 2001).

The study did not include a formal statistical analysis of dose ranging. However, in the efficacy parameters studied, it was possible to discern a trend between dose and response. The general finding in terms of efficacy was that 2 mg could not be distinguished from placebo, while both 4 and 6 mg could be distinguished from placebo to a statistically significant degree and to a greater extent than the 2 mg dose, but not from each other. This pattern was seen in several of the efficacy analysis performed, including sum of pain intensity differences for pain at rest and on movement and differences in pain scores at individual time points. The surrogate markers for duration of action and time for pain score to return to baseline value did not demonstrate a statistically significant difference, but were suggestive of this same trend.

The duration of effect from the different active treatments can be inferred from several of the efficacy parameters studied. In terms of the pairwise comparisons with placebo of pain scores, the 2 mg dose's effect was absent from 2 hours post-dose and for 4 and 6 mg, the effect was absent from 4 hours. These figures depend upon the power of the study, however. From inspecting the plots of the pain scores, the 2 mg dose seems to lose its effect from 2 hours post-dose and the 4 and 6 mg doses from 5 hours for pain on movement and for pain at rest, the effect seems to persist until the end of the 6 hour period. In terms of the time for pain score to return to baseline value, the duration of effect appears to be between 2 and 3 hours for the 2-mg dose, and between 3 and 4 hours for the 4 and 6-mg

doses. This compared with a value of between 1 and 2 hours for the placebo group. The duration of action demonstrated from this study therefore appears to confirm the recommended dosing interval of 3 to 4 hourly and seems to correspond with the distribution / elimination half-life observed in recent pharmacokinetic studies, rather than the longer terminal elimination half-life (U.S. Department of Health and Human Services, 1992).

There was an imbalance between countries in terms of post-operative analgesia. PCA was used for longer in the UK than in France or the Netherlands, leading to a much higher total morphine consumption. Many variables come into play in determining the duration of PCA from standard institutional medical practice to the availability of infusion pumps. However, use of morphine in milligrams per hour was comparable.

The safety profile of hydromorphone was good. There was no statistically significant difference between the four treatment groups in the proportion of patients reporting adverse events. Most adverse events were mild and the relationship to therapy was unlikely or none for approximately 50% of the reported events. Nausea, vomiting and pyrexia were the most common adverse events. Generally, the reports of nausea and vomiting were assessed by the investigator as being probably or possibly related to treatment, whilst reports of pyrexia were assessed as having an unlikely or no relationship to treatment. This is not unexpected as nausea and vomiting are commonly reported side effects associated with opioids. Similar numbers of patients in the hydromorphone 4-mg, 6 mg and placebo groups experienced adverse events commonly reported with morphine; patients in the hydromorphone 2-mg group reported fewer of these events. More specific questioning of patients regarding sedation failed to demonstrate a difference between active and placebo doses. Finally, only five patients withdrew from the study due to adverse events (one in the 2-mg group, three in the 4-mg group, none in the 6-mg group and one in the placebo group).

5.2.7 Conclusions

The relevance of this study to the acute pain setting, in general, is strong, as post-operative knee-replacement patients are an accepted model of moderate-to-severe pain. Svensson (2000) recently highlighted the important nature of the later post-operative period, which follows the immediate recovery from surgery. The population was relatively old (mean age 67.8 years), which is typical of the more general post-surgical population.

Assay sensitivity, the ability to demonstrate the statistically significant activity of an analgesic agent compared to placebo or to another agent, represents a noteworthy achievement for any analgesic study (Schachtel, 1991). Hydromorphone 4 mg and 6 mg were statistically significantly more efficacious than placebo in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery. The tolerability of the three hydromorphone doses was comparable to placebo. These findings confirm impressions gained from more than 50 years of clinical use in North America. Namely, hydromorphone is an effective and safe analgesic in the treatment of acute pain.

The results of this study were given as an oral presentation at the European Congress of Anaesthesiology in Florence, Italy, June 2001. The presenting author was Dr Slappendel. (Slappendel 2001a).

5.3 Active-controlled multiple-dose study in postoperative pain

5.3 Active-controlled multiple-dose study in postoperative pain

5.3.1 Study summary

The title of the study is "A double-blind, repeat-dose, active-control dose-ranging investigation into the efficacy and tolerability of an immediate-release tablet formulation of hydromorphone versus morphine in the treatment of acute post-operative pain". The co-ordinating investigator was Professor D Rowbotham, of Leicester Royal Infirmary, Infirmary Road, Leicester, LE1 5WW.

The objectives of the study were to demonstrate that multiple dosing of hydromorphone was within the range of the efficacy of morphine for the control of pain in post-operative patients who had undergone primary knee replacement surgery and to evaluate the safety of multiple doses of hydromorphone compared with morphine during the post-operative study period.

The methodology was very similar to the single-dose study, being multicentre and double blind, but was repeat-dose and active-controlled and sought equivalence, rather than a statistically significant difference. Patients received doses of hydromorphone 2, 4 or 6 mg or morphine 20 mg every 3-6 hours over a 48-hour treatment period. One additional 50% "rescue" dose of the respective medication was permitted from one to two hours after the first dose of study medication. Assessments of pain, respiratory rate, sedation, nausea and vomiting were made at baseline (0 hours) and intervals throughout the treatment period.

The planned number of patients was 240, 60 in each of the four treatment groups. 271 patients entered the randomised phase, 68 received hydromorphone 2 mg, 71 hydromorphone 4 mg, 67 hydromorphone 6 mg and 65 morphine sulphate 20 mg. A total of 268 patients were included in the "full analysis" set for the principal measure of efficacy.

The patients were in-patients, aged ≥18 years of age, who required post-operative analgesic therapy for pain following primary knee arthroplasty. At baseline, patients were to rate their pain in their knee as ≥ 4 according to the Brief Pain Inventory (BPI).

The efficacy parameters selected were pain at rest, pain on movement and average dose of study medication used. The safety parameters were adverse events, respiratory rate, sedation, nausea and vomiting.

The efficacy results were that the adjusted means for the principal measure, namely the AUC (0-48 h) of pain at rest/48 for the "full analysis" set were 4.6 (hydromorphone 2 mg), 4.0 (hydromorphone 4 mg), 3.5 (hydromorphone 6 mg) and 3.9 (morphine sulphate 20 mg). Each dose of hydromorphone was considered equivalent to morphine if the two one-sided tests for non-inferiority and non-superiority were not significant at the 2.5% level. This was the case and thus it was concluded that the means for all three hydromorphone treatments were within +/- 1.5 of the mean for morphine sulphate 20 mg. The results also implied an ordering between the treatments, with hydromorphone 6 mg as the most effective treatment, hydromorphone 2 mg as the least effective treatment and hydromorphone 4 mg and morphine sulphate 20 mg being very similar.

Analysis of the AUC (0-48 h) of pain at rest/48 for the per-protocol set provided adjusted means of 3.9 (hydromorphone 2 mg), 3.8 (hydromorphone 4 mg) 3.4 (hydromorphone 6 mg) and 3.8 (morphine sulphate 20 mg). The adjusted means were lower than in the "full analysis" set, with hydromorphone 6 mg still the most favoured treatment in terms of efficacy. The adjusted means were lower because the per-protocol set did not include, amongst others, 20 patients who did not provide at least three hours' data and whose pain scores were in general much higher.

For the analysis of the AUC (0-48h) of pain at rest/48 for the "full analysis" set including assessments subsequent to withdrawal, the actual adjusted means for the four treatments were similar, the largest difference being 0.5 for the difference between hydromorphone 2 mg and morphine sulphate 20 mg, in favour of the latter. The reason for the lack of difference between the treatments was that subsequent to withdrawal, the majority of patients were taking other rescue analgesia for their condition.

Analysis of the AUC (0-48h) of pain on movement/48 for the "full analysis" set provided adjusted means of 6.6 (hydromorphone 2 mg), 6.1 (hydromorphone 4 mg), 5.7 (hydromorphone 6 mg) and 5.8 (morphine sulphate 20 mg). The difference between hydromorphone 2 mg and morphine sulphate 20 mg, just failed to reach statistical

significance at the 1.7% level as indicated by the Sidak adjusted 95% confidence interval (-0.02, 1.6).

The proportion of patients requiring the 50% rescue dose was 49%, 45% and 39% for the hydromorphone 2 mg, 4 mg and 6 mg groups respectively. The corresponding figure for morphine sulphate 20-mg was 49%. There was no statistically significant difference between the treatment groups in the time to use of the 50% rescue dose.

The proportion of patients requiring rescue analgesia (other than the 50% rescue dose) during or on withdrawal from the double-blind phase was 34%, 25%, and 25% for the hydromorphone 2 mg, 4 mg and 6 mg groups respectively. The corresponding figure for morphine sulphate 20-mg was 31%. The most common rescue analgesia used was morphine with 48 (18%) patients reporting its use. There was no statistically significant difference ($p=0.22$) between the four treatment groups in the time to first use of rescue medication/second dose of study medication/withdrawal (whichever the sooner). None of the three pairwise comparisons between the three hydromorphone doses and morphine sulphate 20 mg was statistically significant at the 1.7% level (Sidak adjusted 5% level). The mean Kaplan-Meier estimates were 186.4, 292.9 and 228.4 minutes for the hydromorphone 2 mg, 4 mg and 6 mg groups respectively. The corresponding figure for the morphine sulphate 20-mg group was 275.1 minutes.

Including only those patients in the "full analysis" set, the mean average dose of hydromorphone including the 50% rescue dose was 0.54, 0.85 and 1.20 mg/hour for the 2 mg, 4 mg and 6 mg groups respectively. For the morphine sulphate 20 mg group, the mean average dose including the 50% rescue dose was 4.49 mg/hour. Converting the above data into percentages, patients in the hydromorphone 2-mg treatment group received on average 27% of their randomised dose per hour. The equivalent figures for the other three treatment groups were smaller; 21% (hydromorphone 4 mg), 20% (hydromorphone 6 mg) and 22% (morphine sulphate 20 mg).

Adverse events were reported by 42 (62%) patients, 42 (59%) patients, 45 (67%) patients and 38 (58%) patients, respectively for the hydromorphone 2 mg, 4 mg, and 6 mg and morphine sulphate 20 mg dose groups; there was no statistically significant difference between the four groups in the proportion of patients who reported adverse events. Most

adverse events were mild and the relationship to therapy was unlikely or none for approximately 40% of the reported adverse events. Nausea, vomiting, pyrexia and sedation were the most common adverse events. Generally, the reports of nausea, vomiting and sedation were assessed by the investigator as being probably or possibly related to treatment, whilst reports of pyrexia were assessed as having an unlikely or no relationship to treatment. This is not unexpected as nausea, vomiting and sedation are commonly reported side effects associated with opioids. Some of the event rates are suggestive of trends, but statistical testing of these differences failed to demonstrate significance. A total of 14 patients withdrew from the study due to adverse events (3, 5 and 5 in the hydromorphone 2 mg, 4 mg and 6 mg treatment groups, respectively and one in the morphine sulphate 20 mg treatment group). The serious adverse events reported by patients treated with hydromorphone during the double-blind phase of the study were all considered to have an unlikely or no relationship to study medication by the investigator. There were no clinically significant differences in respiratory rate, level of sedation or nausea and vomiting gradings between the four treatment groups.

The study concluded that hydromorphone 2mg, 4mg and 6mg were considered equivalent to morphine 20mg in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery. Efficacy increased with increasing doses, the 6 mg dose being statistically significantly more potent than the 2 mg dose. The 4-mg dose was closest in efficacy to the morphine sulphate 20-mg dose, suggesting an equipotency ratio of 5 for this setting. The tolerability of the three hydromorphone doses was comparable to morphine sulphate 20 mg. These findings confirm impressions gained from more than 50 years of clinical use in North America. Namely, hydromorphone is an effective and safe analgesic in the treatment of acute pain.

5.3.2 Introduction

This study was designed as a direct successor to the single-dose study in postoperative pain. Consequently, the same doses of hydromorphone and the same patient population and treatment procedures were used. The major distinction between the two studies is that the multiple-dose study examined a dosing period of two days, as opposed to the six-hour study period in the single-dose study, and the comparator in the multiple-dose study was morphine instead of placebo. The dose of morphine (20 mg) was selected to represent

clinical practice and to be equipotent to 4 mg of hydromorphone, assuming an equipotency ratio of 1:5.

Largely, the same countries participated and in many cases, the same centres participated in both studies. The aim was to standardise as much as possible between the two studies and the majority of differences were brought about through practical requirements of dosing for longer intervals. The major difference in dosing regimen was brought about because it was felt that it was inappropriate to impose a fixed dosing regimen of oral opioids in this patient population. Therefore, after the initial dose, dosing was on a flexible "three to six hourly as required" basis. Additionally, a half-strength "rescue" dose was added between the first dose and the next possible dose at three hours after the first dose. This was added because of concerns over the possibility of high dropout rates in a two-day study in this setting, especially during the first "settling in" part of the study. Additionally, this change was made since the statistical analysis of this study was based on equivalence rather than difference, and it was considered more important to minimise the dropout rate in order to achieve as high as possible completion rate for patients "per protocol" (CPMP 1999, Jones 1996).

One other difference between the two studies was brought about because of a perceived weakness in the single-dose study – namely, a lack of a qualifying pain score at the time of randomisation. Through adding a qualifying pain score, patients are more likely to comply with the perceived need for pain to be of moderate to severe in its severity, and thus be appropriate for the administration of an oral opioid. The particular value selected was greater than, or equal to four on an 11-point pain scale. This threshold should have resulted in the omission of patients with only mild pain (Serlin 1995). Additionally, having patients start the study with a higher pain score makes it easier to detect differences between treatments. The imposition of a qualifying pain score had some practical consequences, however, since it was important to avoid the scenario of repeat assessments of patients until the point at which the pain score was high enough for them to qualify for the study.

As an equivalence study, there was a requirement to pre-specify what would be considered to be a clinically significant change in the primary efficacy endpoint (pain score as reported by the patient). The pain scale was the 11-point numerical one used in the single-dose study and the clinically equivalent range agreed was ± 1.5. This value was agreed through consultation with opinion leaders during the planning of the study. Other values have been

proposed for a clinically equivalent range (see section 5.3.6). The problem is that the clinically equivalent range on a subjective rating scale is impossible to define. Various attempts have been made to do this, especially in the area of quality of life assessments, but the arguments are essentially circular, since the question is based on a subjective assessment on another subjective assessment.

5.3.3 Objectives

The objectives of the study were:

- To demonstrate that multiple dosing of hydromorphone was equivalent to morphine for the control of pain in postoperative patients who had undergone primary knee replacement surgery.
- To evaluate the safety of multiple doses of hydromorphone compared with morphine during the post-operative study period.

5.3.4 Methods

This was a multicentre, phase II, randomised, double blind, active-control, parallel-group equivalence study. The study was conducted at 27 centres in the United Kingdom, Eire, Netherlands and France. Twelve centres were common to the single and multiple-dose postoperative pain studies. The planned sample size was 200 patients receiving study medication following entry into the study (50 patients in each of the four study treatment groups). A planned blinded re-estimation of sample size was performed after 50 patients completed treatment in order to re-evaluate the number of patients required to enter the study. This resulted in the sample size increasing to 240 patients.

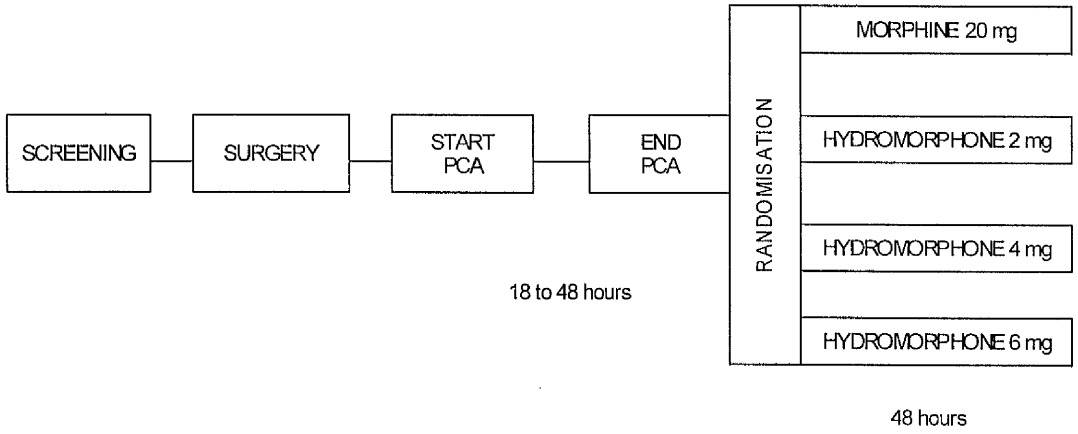
5.3.4.1 Patient selection

The selection criteria for patients were identical to the single-dose study.

5.3.4.2 Study procedures

A diagram of the study design is given below:

Figure 14. Multiple-dose postoperative pain study design



The consent, screening and baseline procedures were identical to the single-dose study, with the exception of the qualifying pain score required in this study. Each patient underwent the baseline study assessment of pain intensity (using an 11-point rating scale ranging from 0 = "no pain" to 10 = "pain as bad as you can imagine"). Patients with a score of four or more for pain at rest were then entered into the study; patients not meeting this criterion left the study and received appropriate medical care. Patients were not informed in advance of what score was necessary to enter the study. Each patient had their pain scored at baseline on one occasion only. The randomisation process was identical to the single-dose study. Assessments of pain, respiratory rate, sedation, nausea and vomiting were repeated at intervals throughout the scheduled forty-eight hour study treatment period. Assessment of pain at rest preceded assessment of pain on movement at each timepoint in the same way as described for the single-dose study. After the first dose, assessments were performed at 30 minutes and then hourly for the first six hours. After 6 hours the assessments were performed every 3 hours, with a maximum of 6 hours between assessments. These were the recommended timings, but they did not have to be strictly adhered to. An assessment must have preceded any administration of study medication, including the 50% "rescue" dose. The arrangements for how physiotherapy interfered with pain assessments were the same as in the single-dose study. Assessments continued on a 3- hourly basis for the duration of the study, irrespective of whether or not the patient continued to receive study medication. If

patients were sleeping when an evaluation was due, they could be roused in order to complete the evaluation.

One minor change from the single-dose study was that in this study, instead of using diclofenac for post-operative NSAID treatment, the French centres used 50-mg i.v. doses of ketoprofen. An 8-hour washout period was required between the last dose of ketoprofen and the baseline pain assessment. Another modification from the single-dose study was that in addition to ondansetron, cyclizine could be used in the post-randomisation phase of the study to treat nausea if a sufficient response to ondansetron had not been achieved.

If the patient requested further analgesia between the first and second dose of study medication, a single 50% "rescue" dose of the study medication could be administrated in addition to the planned 3-6 hourly-when-required regimen. The 50% "rescue" dose could not be administered within the first hour of receiving the first dose of study medication. The choice of the one-hour interval prior to use of the "rescue" dose was based on the known pharmacokinetics of the respective immediate-release formulations, the known onset of action from the single-dose study and from established clinical practice in the use of oral opioids. Assessments then continued with the next dose of medication administered, if required, at the scheduled time point. Further requests for "rescue" analgesia resulted in the patient being withdrawn from the study.

Patients could be withdrawn at any time during the study treatment period (e.g. because of lack of efficacy or tolerability problems with the study medication). If a patient was withdrawn, they immediately had their vital signs recorded and underwent a physical examination, pain assessment and had their status assessed. If the patient did not withdraw consent then the pain assessments were to be continued as per protocol. At the point of withdrawal the patient was to receive the rescue analgesia considered appropriate within the individual hospital (e.g. either re-commencement of morphine therapy with the PCA system or initiation of other parenteral/oral analgesic therapy). The time of re-medication was recorded.

The tolerability for all recruited patients was to be monitored throughout the study period by recording the adverse events experienced. In addition, respiratory rate, sedation, nausea and vomiting were to be assessed at hourly intervals throughout the first 6 hours of the study

and then every 3 hours. Sedation and nausea were assessed using a 4-point scale. The sedation scale was the same as was used in the single-dose study and the nausea scale was the same as was used for all adverse events in the single-dose study.

5.3.4.3 Study assessments

Table 41 below details the timing of the assessments made in the study.

Table 41. Study schedule

Assessment/procedure	Screening	Surgery	Start PCA	End PCA*	Baseline	First dose	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	Every 3–6 h	24 h	Every 3–6 h	48 h
Inclusion/exclusion criteria	x																
Medical history	x																
Physical examination	x																x
Concomitant treatment	x														x		x
Consent	x																
NSAIDs		x															
4 hours of oral intake				x													
2 hours of pain control				x													
Assessment of nerve blockade				x													
Patient requests analgesia					x												
Pain at rest					x		x	x	x	x	x	x	x	x	x	x	x
Pain on movement					x			x	x	x	x	x	x	x	x	x	x
Respiratory rate, nausea, vomiting, sedation					x		x	x	x	x	x	x	x	x	x	x	x
Study medication						x				[redacted]							
Rescue dose								[redacted]									
Adverse events													x		x		x

NSAIDs: Non-steroidal anti-inflammatory drugs

PCA: Patient controlled analgesia

* 18-48 hours post-operative

5.3.4.4 Study medication, blinding and randomisation

Patients received either hydromorphone 2 mg, 4 mg or 6 mg or morphine 20 mg, as an instant-release tablet within a capsule (for blinding purposes) orally. Patients could also receive rescue medication containing 50% of the full dose of hydromorphone/morphine, as appropriate. The study medication consisted of brown capsules (size 0) containing 2 mg hydromorphone, 4 mg hydromorphone, 6 mg hydromorphone or 20 mg morphine. In addition, the following doses of rescue medication were supplied: 1 mg hydromorphone, 2 mg hydromorphone, 3 mg hydromorphone or 10 mg morphine.

Sufficient medication supplies were packed and labelled for 600 patients in total (150 patients in each of the four treatment groups). The repeat dose of medication made available for each patient was packed in bottles (16 capsules per bottle). In addition, a single dose of rescue medication was supplied to each patient in a separate sachet and labelled "rescue medication".

5.3.4.5 Data entry and statistical analysis

The same procedures for data entry and quality assurance were used as for the single-dose study. A random sample of 17 patients had all their information checked. The error rates were 0.05% for adverse events, 0.04% for withdrawal information, 0.09% for randomisation number records, 0.01% for study medication and ≤0.01% for the principal measure of efficacy. The error rates were considered to be satisfactory and any discrepancies found were amended before analysis.

Any one of the three hydromorphone regimens was to be considered equivalent to morphine 20 mg, if the 95% two-sided confidence interval for the treatment difference, measured using the AUC (0-48 h) for pain at rest/48 (principal measure of efficacy) fell wholly within the interval ± 1.5.

For all efficacy variables 95% two-sided confidence intervals (with Sidak adjustment i.e. 98.3% intervals (Sidak 1967) for the three comparisons) for the difference between each hydromorphone dose and morphine 20 mg were calculated.

The "full analysis" set (referred to as the intent-to-treat efficacy analysis in the protocol) included all patients with data recorded for at least one hour within the post-baseline phase. Patients who withdrew from the study had their last observed value for the relevant efficacy variable carried forward for all time periods subsequent to withdrawal in all analyses. For all analyses, endpoint was defined as the last assessment prior to withdrawal from the study. In all the above analyses, any patients with treatment administration errors were to be analysed according to the treatment to which they were randomised. All efficacy variables were analysed using this set.

Because this was an equivalence study a per-protocol analysis was also performed. The per-protocol analysis set was to include all patients in the "full analysis" set excluding patients with major protocol violations and deviations. Any difference between this analysis and the analysis involving the "full analysis" set was explored and explanations identified. All relevant protocol deviations were assessed under blind conditions and documented. Only the analyses relating to the principal measure of efficacy were analysed using this set. All patients taking at least one dose of study medication were included in the analysis of safety. No assessments were excluded from this set.

The treatment groups were assessed for comparability with respect to baseline information, in particular the total dose of morphine administered as PCA prior to stopping, the time from stopping PCA to taking study medication, use of an NSAID between the operation and randomisation, whether the patient received a general or regional anaesthetic and use of anti-emetic medication prior to randomisation. Any clinically significant difference was accounted for in the subsequent analysis.

The principal measure of efficacy was the AUC (0-48h) for pain at rest/48. The AUC was calculated using the trapezoidal rule. Exact timings in relation to the first dose of study medication were used for the AUC calculation for all assessments after randomisation. All baseline assessments were taken as time 0, irrespective of the exact timing in relation to the first dose. If data for less than 48 hours was provided then the last observed value was carried forward up to 48-hour time point. Data recorded after 48 hours was ignored in the AUC analysis. The reason for dividing the AUC value by 48 was so the value could easily be interpreted based on the original BPI scale. If two assessments were recorded at exactly the same time then the worst of the recorded pain scores was used in the analysis.

The actual approach to the testing for equivalence was to follow a two-stage procedure. Firstly non-inferiority was investigated. A stepped approach was taken, where the morphine 20-mg group was initially compared with the hydromorphone 6-mg group. Providing that non-inferiority of hydromorphone 6 mg against morphine 20 mg was proven, then hydromorphone 4 mg was to be compared with morphine 20 mg and if non-inferiority was again confirmed, hydromorphone 2 mg was to be tested against morphine 20 mg. At each stage non-inferiority was inferred if the treatment difference (hydromorphone – morphine 20 mg) was significantly less than 1.5 (one-sided at the 2.5% level). A negative difference favoured hydromorphone. The second part (testing for non-superiority) was to be performed if non-inferiority was inferred for one or more hydromorphone dosing regimens. Again a stepped approach was to be taken where the morphine 20-mg group was compared initially with hydromorphone 2 mg. If non-superiority was proven, hydromorphone 4 mg was to be tested against morphine 20 mg, and if this also implied non-superiority, hydromorphone 6 mg was to be tested against morphine 20 mg for non-superiority. At each stage non-superiority was to be inferred if the treatment difference was significantly greater than -1.5. Control of the overall type I error for multiplicity was achieved by following a closed test procedure for each part. Non-inferiority testing was of prime interest and had an overall type I error of 2.5%. If equivalence (i.e. both non-inferiority and non-superiority) was proven at more than one dose of hydromorphone, an informal approach based on examining mean responses and incidence of adverse events was to be used to determine the most efficacious dose of hydromorphone.

The testing procedure as described above was applied to an analysis of covariance (Armitage 1987, p.282-95) with factors for treatment and country with the baseline value for pain at rest used as a covariate. The 95% two-sided confidence interval (98.3% after adjusting for multiple testing) was also calculated for the difference between the adjusted means for each hydromorphone dose and morphine 20 mg. An additional analysis, including a factor for the treatment-by-country interaction, was performed. If this interaction was significant at the 10% level, the source of the interaction and its impact on treatment equivalence was assessed.

As it was anticipated that few patients were to be recruited in Eire, these patients were pooled with patients recruited from the United Kingdom in the analysis.

The 95% two-sided confidence intervals (with Sidak adjustment for the three comparisons) for the difference between the adjusted means for each hydromorphone dose and morphine 20 mg were also calculated for the AUC (0-48h) for pain on movement/48. The adjusted means were estimated using the same approach as for the principal measure with the score at baseline for the variable used as a covariate (no additional analysis, including a factor for the treatment-by-centre interaction, was performed) although no actual equivalence region was defined.

The average dose (mg/hr) of study medication (including the 50% "rescue" dose if appropriate) received for each patient during the study for each treatment regimen was tabulated, in order to investigate the impact of the flexible dosing regimen aspect of the study.

Mean profiles of pain at rest and pain on movement by treatment were provided for the "full analysis" set. Because many of the later assessments were not recorded at set time points, values for each patient were calculated on an hourly basis, based on the exact timing of the assessments in relation to the first dose of study medication. In each case the nearest assessment to each hourly timepoint was taken. If two assessments were equally near, the earliest recorded assessment was taken.

Adverse event data was handled in the same way as the single-dose study. The difference between the treatment groups in the proportion of patients with adverse events was compared using the chi-square test (Armitage 1987, p.205-9). If the overall test was significant at the 5% level then pairwise comparisons were performed for each hydromorphone dose against morphine 20 mg.

Reason for and time of withdrawal were reported. The time to withdrawal was compared between treatment groups using the logrank test. Pairwise comparisons were performed for each hydromorphone dose against morphine 20 mg with Sidak adjustment. A graph of the Kaplan-Meier estimates for each treatment group of time to withdrawal was provided.

Changes from baseline to endpoint for respiration rate were tabulated by treatment group with the 95% confidence intervals with Sidak adjustment for the pairwise differences between each hydromorphone dose and morphine 20 mg.

The sedation level and degree of nausea at endpoint were tabulated by treatment group. The percentage of patients scoring zero on each of the respective scales were calculated with the 95% confidence intervals with Sidak adjustment for the pairwise differences for each hydromorphone dose against morphine 20 mg.

The number of occurrences of vomiting during the double-blind phase was tabulated by treatment group. The percentage of patients not reporting any occurrences were calculated with the 95% confidence intervals with Sidak adjustment for the pairwise differences for each hydromorphone dose against morphine 20 mg.

Assumption checking regarding the distribution of data was carried out in the same way as for the single-dose study.

Any one of the three hydromorphone regimens was to be considered equivalent to morphine sulphate 20 mg, if the 95% two-sided confidence interval for the treatment difference, measured using the AUC (0-48h) for pain at rest/48 (principal measure of efficacy) fell wholly within the interval ±1.5. The original sample size in the study was 50 patients per treatment group. Assuming the variability (S.D.) to be 2.0 (estimated from a previous study (Baird 1995)) and 90% power, and a true difference of zero between hydromorphone 4 mg and morphine 20 mg and a difference of 0.25 in favour of hydromorphone 6 mg over morphine 20 mg then 41 evaluable patients per group were required (if this difference was zero, power was 85%, which was the minimum power). Power referred to significant non-inferiority of the 4 mg and 6 mg doses and was found by multiplying the power for each of these comparisons. A two-sample t-test (Armitage 1987,106-8) (δ=1.5) was used for the calculation.

After 52 patients had completed the study, the variability for the principal measure was re-estimated to be 2.24. This was calculated by taking the root mean square error from the analysis of covariance model with factors for treatment group and country with baseline as a covariate. This root mean square error was the sole output from a program that accessed the

treatment code (Peace 1993). An appointed independent person within the Biostatistics and Data Management department, who had access to the randomisation code, ran this program. A member of the Company's Quality Assurance department witnessed the running of this program. Using the revised variability and 90% power, and assuming a true difference of zero between hydromorphone 4 mg and morphine sulphate 20 mg and a difference of 0.25 in favour of hydromorphone 6 mg over morphine sulphate 20 mg it was estimated that 60 evaluable patients per group were required. The methodology used to obtain the new sample size estimate was slightly different to that used for the original calculation in the protocol. This revised and more precise approach allowed for the correlations between the paired comparisons in the test procedure (Channon 2000).

The actual variability estimated from the root mean square error (MSE) from the analysis of covariance was 2.16 for the "full analysis" set. The corresponding figure for the per-protocol set was 1.92.

5.3.5 Results

A total of 377 patients were screened for entry into the study between 5 July 1999 and 27 March 2000 of whom 271 actually took study medication. Of the 271 patients randomised, 172 completed the study. Patients were recruited into the study from four countries. Table 42 below gives the number of patients completing and entering the double-blind phase within each country:

Table 42. Summary of number of patients completing and entering the double-blind phase by centre within each country

Country	Treatment group				
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg	Overall
Eire	-	1/1 (100%)	1/1 (100%)	-	2/2 (100%)
France	13/18 (72%)	14/18 (78%)	14/17 (82%)	14/17 (82%)	55/70 (79%)
Netherlands	11/25 (44%)	15/25 (60%)	11/23 (48%)	13/24 (54%)	50/97 (52%)
United Kingdom	15/25 (60%)	19/27 (70%)	15/26 (58%)	16/24 (67%)	65/102 (64%)

Withdrawals and reason for withdrawal, as recorded by the investigator, are summarised in the Table 43 below. There was no statistically significant difference between treatment groups in the time to withdrawal (p=0.43), patients in the hydromorphone 2 mg treatment

group had the lowest mean time to withdrawal (1227.3 minutes) and patients in the hydromorphone 6 mg treatment group had the highest time (1691.2 minutes). The proportions withdrawing due to lack of efficacy were 24%, 14% and 12% in the hydromorphone 2 mg, 4 mg and 6 mg groups compared to 20% in the morphine 20 mg group. Many patients who were classified as having withdrawn due to protocol violation were those requiring rescue analgesia. Additionally, withdrawal of consent could have been linked with the patient's perception of insufficient efficacy. Therefore, it is probably more appropriate to consider withdrawals as a whole, rather than deal with each sub-category.

Table 43. Summary of patient withdrawals during the double-blind phase

Reason for withdrawal	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Adverse event	3	5	5	1
Lack of efficacy	16	10	8	13
Protocol violation	4	5	9	5
Administrative reasons	-	-	-	1
Withdrawal of consent	6	2	4	2
Total withdrawn	29 (43%)	22 (31%)	26 (39%)	22 (34%)
Time to withdrawal (min)				
Mean[b]	1227.3	1632.9	1691.2	1460.1
se	78.2	76.0	96.1	83.8
Range	29, 1680	70, 1981	11, 2190	60, 1862
Comparisons of time to withdrawal (logrank test)		χ^2	df	p[a]
Overall		2.79	3	0.43
Hydromorphone 2 mg versus morphine 20 mg		1.18	1	0.28
Hydromorphone 4 mg versus morphine 20 mg		0.20	1	0.65
Hydromorphone 6 mg versus morphine 20 mg		0.19	1	0.66

[a] Statistically significant if p<0.017 using Sidak adjustment

[b] Kaplan-Meier estimate

A summary of protocol deviations for all patients randomised is provided in Table 44 below.

Table 44. Summary of protocol deviations during the double-blind phase

Deviation[a]	Treatment group				Overall
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20mg	
Major deviations leading to patients being excluded from PP* population					
Withdrew from the study within three hours of the first study medication dose[b]	7	4	3	6	20
Baseline pain at rest assessments more than one hour prior to the first dose of study medication	3	2	1	1	7
Took inadmissible analgesics prior to first dosing with study medication	1	1	2	1	5
Inadmissible analgesics starting during the first 60 minutes of the double-blind phase	-	-	1	1	2
Previous major surgery to affected knee	-	-	1	-	1
Hip (rather than knee) replacement performed	-	1	-	-	1
Baseline pain at rest less than 4	-	-	1	-	1
Number of patients excluded from PP* population	10	8	9	9	36
Major deviations leading to patients being partially excluded from PP* population[c]					
Inadmissible analgesics starting after the first 60 minutes of the double-blind phase prior to completion/withdrawal	4	3	3	5	15
At least one assessment where physiotherapy was performed within 30 minutes of assessment	4	4	3	5	16
At least one occurrence of study medication two hours or less apart	-	1	-	2	3
Number of patients having data partially excluded from PP population	8	8	6	12	34
Number of patients with at least one major deviation	18	15	15	20	68
Other deviations not leading to exclusion of data					
Received PCA for <18 hours	3	6	3	4	16
More than 48 hours between surgery and first study medication dose	1	1	1	3	6
Baseline pain at rest assessments recorded after first dosing of study medication[d]	2	1	1	-	4
50% rescue dose more than three hours after initial dose of study medication	1	-	-	2	3
Study medication taken after withdrawal	-	1	1	-	2
Less than one hour between 50% rescue dose and second study medication dose	-	-	1	-	1
50% rescue dose less than one hour after the first study medication dose	-	1	-	-	1
Number of patients with minor deviations	7	10	6	9	32
Number of patients with at least one deviation	23	21	18	26	88

* PP = "per protocol", [a] Not mutually exclusive, [b] Includes three patients (numbers 432, 443 and 508) who failed to provide efficacy data for at least one hour, so were not included in the "full analysis" set, [c] Assessments subsequent to deviation excluded, [d] The maximum time reported after first dose was 10 minutes

5.3.5.1 Efficacy

A total of 271 patients entered the double-blind phase of the study. Three patients failed to provide data for at least one hour for the principal measure of efficacy, so were not included in the "full analysis" set which included 268 patients. One patient in the morphine 20mg group (number 410) did not have the splint removed after surgery, as a result this patient did not provide any pain-on-movement data.

Regarding demographic information; the treatment groups were relatively well balanced with respect to all variables tabulated as summarised in the Table 45 below:

Table 45. Summary of entry profile for all patients randomised

	Treatment group				
Variable	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20mg	Overall
n	68	71	67	65	271
Mean age ± sd(yr)	67.2 ± 8.4	68.8 ± 8.8	69.1± 9.3	68.3 ± 10.0	68.3 ± 9.1
Female	44 (65%)	51 (72%)	50 (75%)	46 (71%)	191 (70%)
Caucasian	67 (98.5%)	71 (100%)	66 (98.5%)	63 (96.9%)	267 (98.5%)
Mean height ± sd(cm)	165.4 ± 9.0	163.8 ± 11.7	163.3 ± 10.3	165.2 ± 9.0	164.4 ± 10.1
Mean weight ± sd (kg)	79.6 ± 14.5	76.3 ± 13.7	77.3 ± 14.4	76.0 ± 14.4	77.3 ± 14.2

Table 46 presents data on the American Society of Anesthesiologists (ASA) classification, affected limb, details of post-operative analgesia and time from operation to study medication dispensed. The treatment groups were well balanced with respect to these variables.

Table 46. ASA classification, affected limb, details of post-operative analgesia and time from operation to study medication dispensed for all patients randomised

		Treatment group				Overall
		Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg	
Total number of patients		68	71	67	65	271
ASA classification of physical status[a]	I	16	12	15	11	52
	II	42	49	43	43	177
	III	7	9	9	9	34
	Unknown	3	1	2	2	8
Affected knee	Left	33	29	34	37	133
	Right	35	42	32	28	137
	Bilateral	-	-	1	-	1
Knee assessed	Left	33	29	35	37	134
	Right	35	42	32	28	137
Type of prosthesis	Total	60	68	64	61	253
	Unicompartmental	8	3	2	3	16
	Patella and femoral head	-	-	1	1	2
General anaesthetic used	Yes	25	31	27	27	110
	No	43	40	40	38	161
Regional anaesthetic used	Yes	54	48	50	50	202
	No	14	23	17	15	69

There were imbalances between countries with respect to total duration of PCA use and the corresponding time from the operation to the taking of the first study medication dose, ASA classification, type of prosthesis, use of anaesthetics and the use of diclofenac/ketoprofen perioperatively and in the early stages of post-operative management. A total of 23% of patients (with known gradings) were graded III using ASA in the UK+Eire centres compared to 10% in the French centres and 3% in the Dutch centres. The use of general anaesthetics was much more common (83%) in the UK+Eire compared to the centres in mainland Europe (21% use in France and 9% use in the Netherlands). However, regional anaesthetics were only used on 58% of patients recruited in UK+Eire whereas 88% of patients in the Netherlands and 81% of patients in France had regional anaesthetics. Six patients had no information recorded about anaesthetic use, either regional or general. For tabulation purposes these patients were assumed to have taken neither, although this was certainly not the case. Only one patient in the non-French centres did not have a total prosthesis, whereas in France 53 (76%) reported a total prosthesis, 15 (21%) had a unicompartmental prosthesis and 2 (3%) had a patella and femoral head prosthesis. Use of diclofenac/ketoprofen perioperatively or in early post-operative management was more prevalent in France (53% of patients reporting), compared to the Netherlands (31% of patients reporting) and UK+Eire (19% of patients reporting). Patients in the UK+Eire, in general, received PCA morphine over a longer time period compared to patients in the other two countries. The use of morphine in mg/hour was broadly similar across countries. Table 47 below summarises these imbalances.

Table 47. Summary of selected PCA variables by country

Variable	Country			Overall
	France	Netherlands	UK+Eire	
n	70	97	104	271
% graded as ASA grade III (excluding patients with no grades recorded)	10%	3%	23%	13%
% using general anaesthetics	21%	9%	83%	41%
% using regional anaesthetics	81%	88%	58%	75%
% with total prosthesis	76%	100%	99%	93%
% using diclofenac/ketoprofen perioperatively or in early post-operative management	53%	31%	19%	32%
Median (range) morphine dose administered as PCA (mg)	33.5 (2, 104)	31.6 (4, 106)	47.0 (5, 229)	37.0 (2, 229)
Median (range) amount of morphine sulphate administered as PCA per hour (mg/h)	1.40 (0.1, 2.8)	1.65 (0.2, 5.8)	1.65 (0.2, 8.3)	1.60 (0.1, 8.3)
Median total duration of PCA (h)	21.1	20.0	35.2	21.3
Median time from operation to study medication dispensed (h)	23.7	22.8	41.0	24.4

Table 48 below summarises the total amount of morphine administered (including non-PCA) tabulated by whether the single 100 mg rectal dose of diclofenac or 50 mg i.v dose of ketoprofen was given peri-operatively or in early post operative management. Morphine consumption was higher in patients who did not receive the diclofenac/ketoprofen dose. However, this comparison could have been affected by the national differences in the use of NSAIDs and PCA. Since the UK used less NSAIDs and persisted with PCA for longer, this would bias this result towards morphine consumption being greater in the non-NSAID group.

Table 48. Total morphine administered by diclofenac/ketoprofen use

Received diclofenac/ ketoprofen dose	Morphine consumption (mg)				
	n	Mean	Median	sd	Range
Yes	87	36.7	30.0	24.3	4,121
No	184	48.3	42.0	34.3	2,247
Overall	271	44.6	38.0	31.9	2,247

The most commonly reported ongoing diseases were osteoarthritis reported by 94 (35%) patients, localised osteoarthritis reported by 40 (15%) patients, rheumatoid arthritis reported by 25 (9%) patients and arthrosis reported by 22 (8%) patients.

A total of 226 (83%) patients reported previous medications prior to the end of the operation including 123 (45%) patients who received psycholeptics, 112 (41%) patients who used analgesics, 80 (30%) patients who used anti-inflammatory and anti-rheumatic products and 44 (16%) patients who used antibacterials for systemic use. A total of 263 (97%) patients had ongoing concomitant medications (excluding anaesthetics, extra non-PCA doses of morphine and single 100 mg rectal doses of diclofenac or i.v doses of ketoprofen given immediately after the operation) at the end of the operation, including 131 (48%) who were using antibacterials for systemic use and 124 (46%) who started antithrombotic agents. One hundred and sixty nine (62%) patients commenced medications between the end of the operation and randomisation, including 89 (33%) who started antithrombotic agents and 60 (22%) who started antibacterials for systemic use. Sixty-eight (25%) patients commenced medications during the double-blind phase including 12 (4%) patients who took analgesics for reasons other than rescue purpose, either for a headache or pyrexia. In each case, data recorded after the commencement of analgesia were excluded from the per-protocol dataset. A total of 102 (38%) patients commenced anti-emetics between the end of the operation and randomisation with 89 (33%) using ondansetron. Forty-five (17%) patients commenced anti-emetics during the double-blind phase including 42 (16%) patients who used

ondansetron. The percent reporting in the three hydromorphone groups were 16% (2 mg), 18% (4 mg), 21% (6 mg) compared to 11% for the morphine 20 mg group.

Table 49 below summarises the data concerning the interval between doses of study medication. There appears to be a trend towards more frequent dosing with lower doses.

Table 49. Average time between doses (all patients randomised)

Average time between doses	Treatment group			
(h)	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Number who only had one dose	9 (13%)	6 (8%)	7 (10%)	10 (15%)
Number who had more than one dose	59 (87%)	65 (92%)	60 (90%)	55 (85%)
<3	-	-	1	1
3 to <4.5	18	9	8	8
4.5 to <6	12	14	18	10
6 to <7.5	13	16	8	12
7.5 to <9	8	6	8	5
9 to <12	6	15	11	14
12 to <15	-	2	3	2
≥15	2	3	3	3
Median	5.6	6.6	6.4	7.0
Range	3.0,23.1	3.0,23.4	2.9,20.3	2.5,22.8

5.3.5.1.1 "Full analysis" set

For the principal measure of efficacy, namely the AUC (0-48 h) of pain at rest/48 for the "full analysis" set, the treatments were considered equivalent if the two one-sided tests for non-inferiority and non-superiority were significant at the 2.5% level. This was the case and thus it was concluded that the means for all three hydromorphone treatments were within +/- 1.5 of the mean for morphine sulphate 20 mg. The actual adjusted means for the four treatments were 4.6 (hydromorphone 2 mg), 4.0 (hydromorphone 4 mg), 3.5 (hydromorphone 6 mg) and 3.9 (morphine sulphate 20 mg). In the analysis of covariance the terms for treatment group (p=0.047) and country (p=0.002) were statistically significant. The significance of the treatment group effect was particularly influenced by the difference between the hydromorphone 2 mg and 6 mg groups, which was 1.1 in favour of hydromorphone 6 mg. Efficacy increased with increasing doses, the 6 mg dose being statistically significantly more potent than the 2 mg dose.

Mean AUC pain scores were in general larger in the Dutch centres. The treatment group-by-country interaction was not statistically significant (p=0.93), implying that treatment differences were comparable across countries. Table 50 below summarises the data:

Table 50. Analysis of covariance for the AUC (0-48h) of pain at rest/48 ("full analysis" set)

AUC (0-48h) for pain at rest/48[a]	Treatment group			
	Hyd. 2 mg (n=67)	Hyd. 4 mg (n=71)	Hyd. 6 mg (n=65)	Morphine 20 mg (n=65)
Mean ± sd	4.6 ± 2.4	3.9 ± 2.2	3.4 ± 2.0	4.0 ± 2.6
Range	0.1, 10.0	0.8, 10.0	0.1, 8.9	0.3, 9.9
Adjusted mean[b]	4.6	4.0	3.5	3.9
Difference in adjusted means relative to morphine 20mg[c]	0.7	0.1	-0.4	
se (of difference)	0.4	0.4	0.4	
98.3% CI for difference[d]	-0.2, 1.6[e]	-0.8, 0.9	-1.3, 0.5	
p (non-inferiority)[f]	0.014	<0.001	<0.001	
p (non-superiority)[g]	<0.001	<0.001	0.002	

[a] The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = no pain; 10 = pain as bad as you can imagine)

[b] Adjusted for baseline and country

[c] A negative difference favours hydromorphone

[d] Sidak adjusted 95% CI

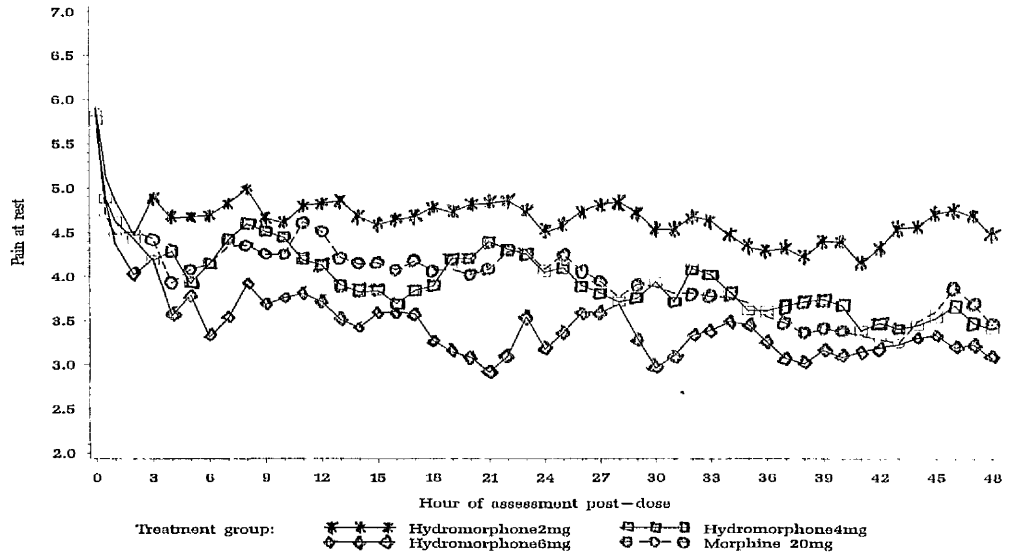
[e] Although the upper limit of the CI is above 1.5, hydromorphone 2mg was considered non-inferior to morphine 20mg. Testing of non-inferiority and non-superiority followed a closed test procedure, whereas the CIs presented have been adjusted for multiplicity and are at the 98.3% level

[f] One sided t-test of null hypothesis hydromorphone – morphine 20mg $\geq$ 1.5 (non-inferior if p<0.025)

[g] One sided t-test of null hypothesis hydromorphone – morphine 20mg $\leq$ 1.5 (non-superior if p<0.025)

Figure 15 below present the mean profile for pain at rest for the "full analysis" set. It clearly shows that in terms of efficacy hydromorphone 2 mg was the least favoured treatment and hydromorphone 6mg the most favoured treatment.

Figure 15. Mean profile for pain at rest ("full analysis" set)



5.3.5.1.2 Per-protocol set

The analysis for the AUC (0-48 h) of pain at rest/48 for the per-protocol set, the actual adjusted means for the four treatments were 3.9 (hydromorphone 2 mg), 3.8 (hydromorphone 4 mg) 3.4 (hydromorphone 6 mg) and 3.8 (morphine sulphate 20 mg) (see Table 51). The adjusted means in general were lower than in the "full analysis" set, with hydromorphone 6 mg still the most favoured treatment in terms of efficacy. The adjusted means were lower because the per-protocol set did not include, amongst others, the 20 patients who did not provide at least three hours data (included in these 20 patients were three patients also excluded from the "full analysis" set as they provided data for less than one hour).

Table 51. Analysis of covariance for the AUC (0-48h) of pain at rest/48 (per-protocol set)

AUC (0-48h) for pain at rest/48[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	58	63	58	56
Mean	4.1	3.8	3.4	3.7
sd	2.1	2.0	1.8	2.5
Range	0.1,9.6	0.8,9.8	0.1,7.1	0.1,9.8
Adjusted mean[b]	3.9	3.8	3.4	3.8
Difference in adjusted means relative to morphine 20 mg[c]	0.2	0.02	-0.3	
se (of difference)	0.4	0.4	0.4	
98.3% CI for difference[d]	-0.7,1.0	-0.8,0.9	-1.2,0.5	
p (non-inferiority)[e]	<0.001	<0.001	<0.001	
p (non-superiority)[f]	<0.001	<0.001	<0.001	

Analysis of covariance	F	df	p
Baseline	33.72	1,228	<0.001
Treatment group	0.72	3,228	0.54
Country	4.15	2,228	0.02
Treatment group-by-country	1.99	6,222	0.07

a The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = no pain; 10 = pain as bad as you can imagine)
b Adjusted for baseline and country
c A negative difference favours hydromorphone
d Sidak adjusted 95% CI
e One sided t-test of null hypothesis hydromorphone – morphine 20 mg ≥ 1.5 (non-inferior if p<0.025)
f One sided t-test of null hypothesis hydromorphone – morphine 20 mg ≤ -1.5 (non-superior if p<0.025)

In the analysis of covariance the term for country (p=0.02) was statistically significant and also the term for treatment-by country interaction was significant at the 10% level (p=0.07). The adjusted means for each treatment group by country are provided in Table 52 below:

Table 52. Adjusted means for the AUC (0-48h) of pain at rest/48 ("per protocol" set)

Country	Adjusted means for AUC (0-48h) for pain at rest/48			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
France	3.7 (n=16)	3.6 (n=16)	3.5 (n=17)	3.6 (n=15)
Netherlands	5.3 (n=21)	3.8 (n=23)	3.8 (n=18)	3.9 (n=21)
UK+Eire	2.8 (n=21)	3.9 (n=24)	3.0 (n=23)	3.7 (n=20)
Overall	3.9 (n=58)	3.8 (n=63)	3.4 (N=58)	3.8 (n=56)

The significant interaction term was influenced by the hydromorphone 2-mg means for the Netherlands and the UK+Eire. Patients who received hydromorphone 6 mg in the UK+Eire centres also seemed to perform better, in terms of efficacy than patients who received the same dose in the other two countries.

5.3.5.1.3 "Full analysis" set including assessments subsequent to withdrawal

For the analysis the AUC (0-48h) of pain at rest/48 for the "full analysis" set including assessments subsequent to withdrawal, the actual adjusted means for the four treatments were similar, the largest difference being 0.5 for the difference between hydromorphone 2

mg and morphine sulphate 20 mg, in favour of the latter (see Table 53). The reason for the lack of difference between the treatments was that subsequent to withdrawal, the majority of patients were taking other rescue analgesia for their condition.

Table 53. Analysis of covariance for the AUC (0-48h) of pain at rest/48 ("full analysis" set but also including assessments subsequent to withdrawal)

AUC (0-48h) for pain at rest/48[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	67	71	65	65
Mean	3.5	3.1	3.1	3.0
sd	1.6	1.2	1.4	1.6
Range	0.1,9.6	0.8,6.5	0.2,6.2	0.3,8.6
Adjusted mean[b]	3.4	3.1	3.2	3.0
Difference in adjusted means relative to morphine 20 mg[c]	0.5	0.1	0.2	
se (of difference)	0.2	0.2	0.2	
98.3% CI for difference[d]	-0.1,1.0	-0.4,0.7	-0.4,0.8	
p (non-inferiority)[e]	<0.001	<0.001	<0.001	
p (non-superiority)[f]	<0.001	<0.001	<0.001	

Analysis of covariance	F	df	p
Baseline	38.52	1,261	<0.001
Treatment group	1.32	3,261	0.27
Country	0.90	2,261	0.41
Treatment group-by-country	0.72	6,255	0.63

a The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = no pain; 10 = pain as bad as you can imagine)
b Adjusted for baseline and country
c A negative difference favours hydromorphone
d Sidak adjusted 95% CI
e One sided t-test of null hypothesis hydromorphone – morphine 20 mg ≥ 1.5 (non-inferior if p<0.025)
f One sided t-test of null hypothesis hydromorphone – morphine 20 mg ≤ -1.5 (non-superior if p<0.025)

The impact of using additional rescue analgesia following withdrawal on reducing the pain scores can be seen in Table 54 below which compares the pain score recorded immediately before withdrawal to the score recorded at the end of the study. Combining all the treatment groups together mean pain scores were reduced by 3.1 from a value of 5.8 immediately prior to withdrawal to a value of 2.7 at the end of the study. Note that pain scores on withdrawal were much lower in the hydromorphone 6-mg group.

Table 54. Mean (+ sd) changes in pain at rest scores immediately prior to withdrawal to the end of study

Assessment	Treatment group				
	Hyd. 2 mg (n=26)	Hyd. 4 mg (n=20)	Hyd. 6 mg (n=25)	Morphine 20 mg (n=20)	Overall (n=91)
Prior to withdrawal	6.6 ± 2.6	6.4 ± 2.8	4.2 ± 3.3	6.1 ± 3.5	5.8 ± 3.1
End of study	2.3 ± 1.9	3.1 ± 2.5	3.3 ± 2.6	2.3 ± 2.0	2.7 ± 2.3
Change	-4.3 ± 3.2	-3.3 ± 3.2	-0.9 ± 2.9	-3.9 ± 2.9	-3.1 ± 3.3

5.3.5.1.4 Other analyses

For the AUC (0-48h) of pain on movement/48 for the "full analysis" set, the actual adjusted means for the four treatments were 6.6 (hydromorphone 2 mg), 6.1 (hydromorphone 4 mg), 5.7 (hydromorphone 6 mg) and 5.8 (morphine sulphate 20 mg). In the analysis of covariance the term for treatment group ($p=0.04$) and country ($p<0.001$) were statistically significant. The difference between hydromorphone 2 mg and morphine sulphate 20 mg, just failed to reach statistical significance at the 1.7% level as indicated by the Sidak adjusted 95% confidence interval (-0.02, 1.6). As for the AUC analyses involving pain at rest, means were in general larger in the Netherlands. Table 55 below summarises the data:

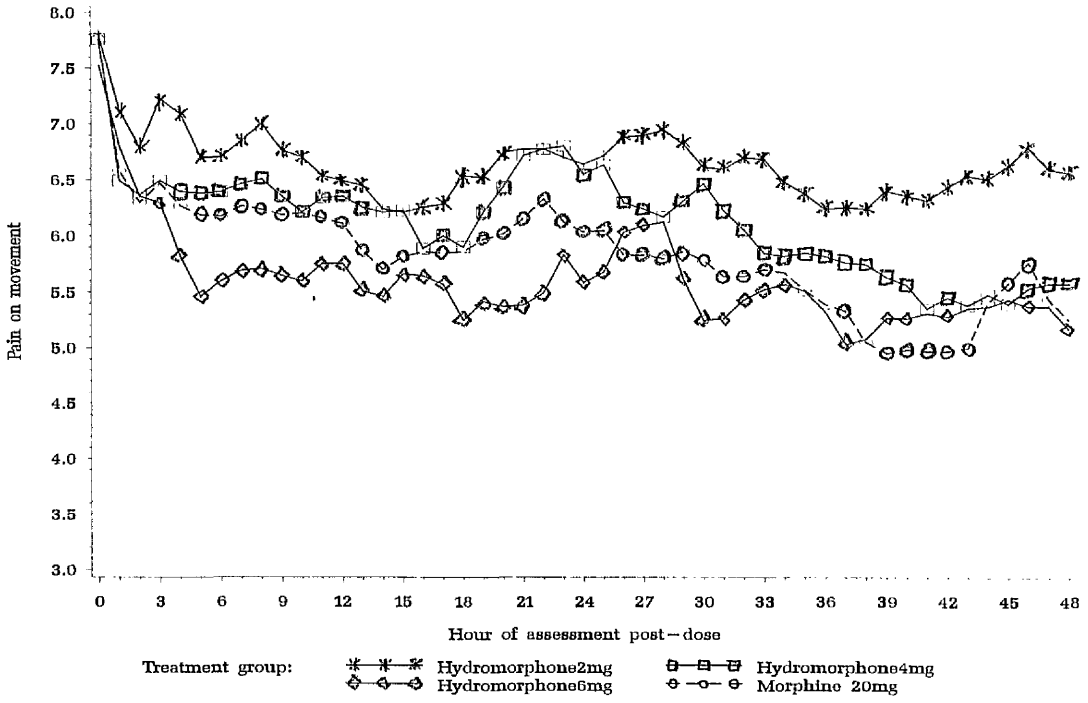
Table 55. Analysis of covariance for the AUC (0-48h) of pain on movement/48 ("full analysis" set)

AUC (0-48h) for pain on movement/48[a]	Treatment group			
	Hyd. 2 mg (n=67)	Hyd. 4 mg (n=71)	Hyd. 6 mg (n=65)	Morphine 20 mg (n=64)
Mean± sd	6.6 ± 2.2	6.1 ± 2.0	5.6 ± 2.0	5.8 ± 2.2
Range	1.5, 10.0	2.3, 10.0	1.3, 9.9	1.5, 10.0
Adjusted mean[b]	6.6	6.1	5.7	5.8
Difference in adjusted means relative to morphine 20mg[c]	0.8	0.3	-0.1	
se (of difference)	0.3	0.3	0.3	
98.3% CI for difference[d]	-0.02, 1.6	-0.5, 1.1	-0.9, 0.7	

[a] The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = no pain; 10 = pain as bad as you can imagine)
[b] Adjusted for baseline and country
[c] A negative difference favours hydromorphone HCl
[d] Sidak adjusted 95% CI

Figure 16 below presents the mean profile for pain on movement for the "full analysis" set. They clearly show that hydromorphone 2 mg was the least favoured treatment and hydromorphone 6 mg the most favoured treatment in terms of efficacy.

Figure 16. Mean profile for pain on movement ("full analysis" set)



The proportion of patients requiring the 50% rescue dose was 49%, 45% and 39% for the hydromorphone 2 mg, 4 mg and 6 mg groups respectively. The corresponding figure for morphine sulphate 20 mg was 49%. There was no statistically significant difference between the treatment groups in the time to use of the 50% rescue dose (Table 56).

Table 56. Time to use of 50% rescue dose (all patients randomised)

Time to use of 50% rescue dose (min)[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Number of patients reporting use of 50% rescue dose	33 (49%)	32 (45%)	26 (39%)	32 (49%)
<60	-	1	-	-
60-89	20	14	13	12
90-119	6	5	3	6
≥120	7	12	10	14

Comparisons (logrank test)	χ^2	df	p[b]
Overall	1.38	3	0.71
Hydromorphone 2 mg versus morphine 20 mg	0.27	1	0.61
Hydromorphone 4 mg versus morphine 20 mg	0.01	1	0.91
Hydromorphone 6 mg versus morphine 20 mg	0.52	1	0.47

Mean[c]	608.8	131.8	126.8	780.3
se	63.4	5.1	4.3	233.5

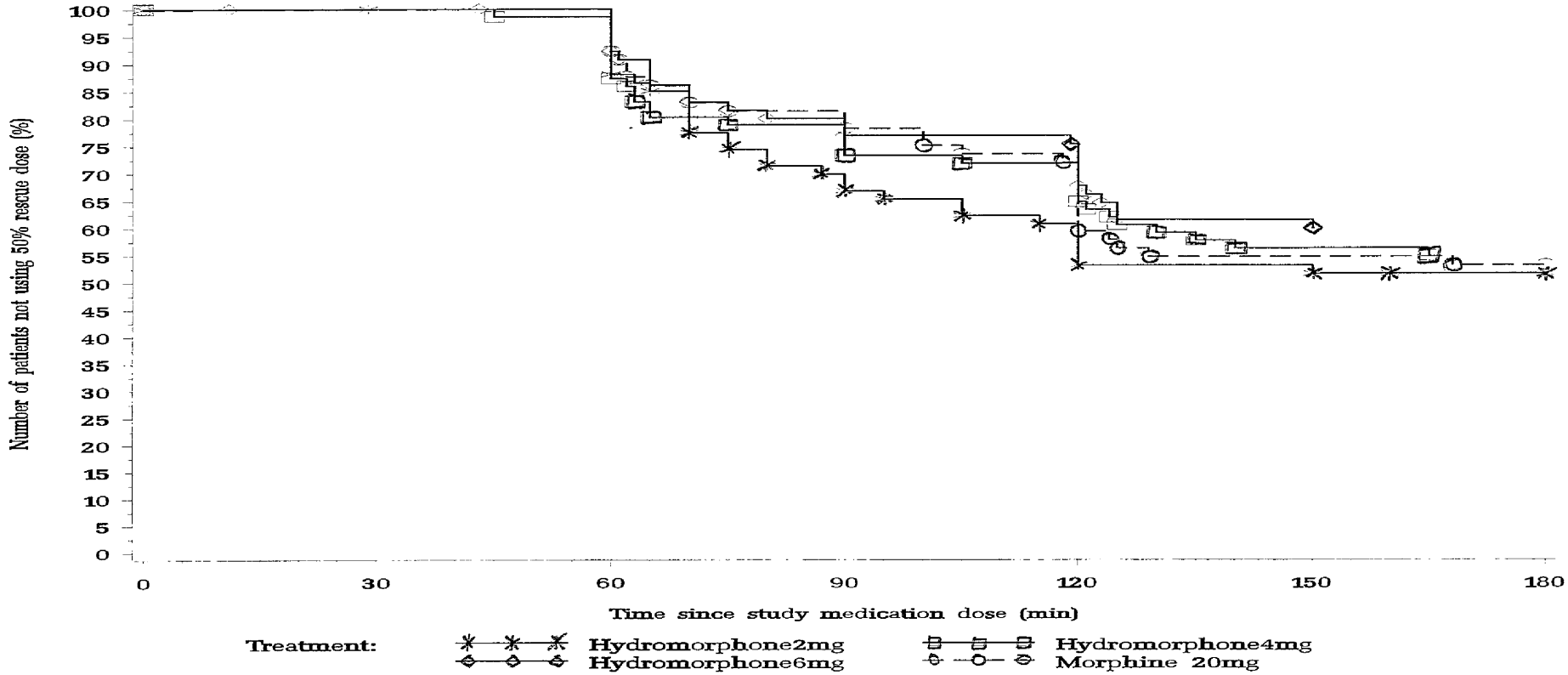
a Time calculated from time of first dose of study medication

b Statistically significant if p<0.017 by Sidak adjustment

c Kaplan-Meier estimate. Patients who did not use the 50% rescue dose had their time censored at the time of their withdrawal or 180 minutes post-dose whichever was the sooner. Excluding the three patients (one in hydromorphone 2 mg group and two in the morphine 20 mg group) who used their 50% rescue dose after their second dose of study medication the mean (se) Kaplan-Meier estimates were 117.9 (4.7) for hydromorphone 2 mg and 133.2 (5.3) for morphine 20 mg

Figure 17 presents the Kaplan-Meier estimates for each treatment. This illustrates that more patients required the 50% rescue dose in the hydromorphone 2-mg group from 70 minutes post-baseline onwards.

Figure 17. Kaplan-Meier estimates for time to use of 50% rescue dose (all patients randomised)



The proportion of patients requiring rescue analgesia (other than the 50% rescue dose) during or on withdrawal from the double-blind phase was 34%, 25%, and 25% for the hydromorphone 2 mg, 4 mg and 6 mg groups respectively. The corresponding figure for morphine sulphate 20 mg was 31%. The most common rescue analgesia used was morphine with 48 (18%) patients reporting its use (Table 57).

Table 57. Details of rescue analgesia used during or on withdrawal from the double-blind phase (all patients randomised)

Analgesia[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Number of patients reporting the use of rescue analgesia	23 (34%)	18 (25%)	17 (25%)	20 (31%)
Buprenorphine	-	1	-	-
Codeine	-	-	2	-
Diclofenac	3	1	3	2
Dihydrocodeine	-	1	2	2
Haloperidol	1	-	1	-
Ibuprofen	-	-	1	-
Ketoprofen	1	1	2	2
Meloxicam	2	2	1	2
Morphine	15	11	9	13
Naproxen	-	-	1	-
Paracetamol	7	4	5	4
Paracetamol+codeine	3	3	-	1
Paracetamol+dextropropoxyphene	1	1	2	1
Paracetamol+dihydrocodeine	1	-	-	-
Piritramide	1	-	-	-
Propacetamol	2	1	2	1
Tramadol	2	2	1	-
Tylex	-	-	-	1

a Not mutually exclusive

Including only those patients in the "full analysis" set, the mean average dose of hydromorphone including the 50% rescue dose was 0.54, 0.85 and 1.20 mg/hour for the 2 mg, 4 mg and 6 mg groups respectively. For the morphine sulphate 20 mg group, the mean average dose including the 50% rescue dose was 4.49 mg/hour. Converting the above data into percentages, patients in the hydromorphone 2-mg treatment group received on average 27% of their randomised dose per hour. The equivalent figures for the other three treatment groups were smaller; 21% (hydromorphone 4 mg), 20% (hydromorphone 6 mg) and 22% (morphine sulphate 20 mg).

5.3.5.1.5 Statistical/analytical issues

Due to the nature of the analysis, patients who withdrew from the analysis had their last recorded pain score prior to withdrawal carried forward to 48 hours for purposes of

calculating the AUC. As illustrated in Table 58 below the mean AUC for pain at rest for the patients who withdrew early from the study was much larger than for the other patients in the "full analysis" set:

Table 58 Mean AUC (0-48h) of pain at rest/48 for early withdrawals versus other patients ("full analysis" set)

Patient population	Means for AUC (0-48h) for pain at rest/48				
	Hyd. 2mg	Hyd. 4mg	Hyd. 6mg	Morphine 20mg	Overall
Early withdrawals[a]	8.1 (n=6)	9.2 (n=4)	6.9 (n=1)	7.5 (n=6)	8.1 (n=17)
Other patients	4.3 (n=61)	3.6 (n=67)	3.4 (n=64)	3.6 (n=59)	3.7 (n=251)

[a] Includes patients who withdrew within three hours of first dosing

As a result of excluding the very early withdrawals, the variability decreased and therefore the Sidak adjusted confidence intervals were much narrower in the per-protocol dataset.

Using the interpolation technique as advocated by Channon (2000), it was possible to calculate the equipotent dose of hydromorphone against morphine sulphate 20 mg, assuming an equivalence zone of +/- 1.5. For the principal measure of efficacy, the equipotent doses were 4.2 mg for the "full analysis" set and 4.1 mg for the per-protocol set. For AUC (0-48 h) of pain on movement/48 the equipotent doses for the "full analysis" set was much higher, namely 5.5 mg.

5.3.5.1.6 Efficacy conclusions

Hydromorphone 2 mg, 4 mg and 6 mg, when dosed on a flexible basis and assuming a clinical equivalence zone of ± 1.5, were considered equivalent to morphine 20 mg in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery. Efficacy increased with increasing doses, the 6 mg dose being statistically significantly more potent than the 2 mg dose.

5.3.5.2 Safety

Table 59 below summarises the total dosage (in mg including the 50% rescue dose) of study medication for each of the four treatment groups for the time that each individual patient remained in the study. The exposure, proportional to the dose administered on each occasion, appears broadly similar across the groups. It should be stressed, however, that the time to withdrawal for patients in the hydromorphone 2-mg group was shorter than the other

three treatment groups. Thus, the time over which dosing took place is not accounted for in this presentation of the data.

Table 59. Total dosage of study medication taken – all patients randomised

Total dosage (mg)	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
n	68	71	67	65
Mean	11.0	21.5	31.5	101.2
sd	6.4	12.0	15.9	62.8
Range	2, 28	4, 66	6, 63	20, 330
Total	747	1528	2112	6580

Of the 271 patients randomised to study medication, 68, 71, 67 and 65 patients received hydromorphone 2 mg, 4 mg and 6 mg and morphine sulphate 20 mg respectively. A summary of exposure, based on the total number of doses taken is provided in Table 60 below.

Table 60. Extent of exposure (all patients randomised)

Total number of doses taken (excluding 50% rescue dose)	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
1	9	6	7	10
2	11	10	9	8
3 to 4	10	16	14	14
5 to 6	11	18	14	18
7 to 8	17	12	16	8
9 to 12	9	8	7	6
13 to 16	1	1	-	1
Median (all patients)	5.0	5.0	5.0	5.0
Range	1,14	1,16	1,10	1,16
Sum	357	366	339	313

A total of 123 (45%) of patients took the 50% rescue dose. This included 33 (49%) patients in the hydromorphone 2 mg treatment group, 32 (45%) patients in the hydromorphone 4 mg treatment group, 26 (39%) patients in the hydromorphone 6 mg treatment group and 32 (49%) patients in the morphine sulphate 20 mg treatment group.

Three patients completed the study despite only taking one dose of study medication. The patients involved were numbers 417 (morphine sulphate 20 mg), 575 (hydromorphone 2 mg) and 590 (hydromorphone 4 mg). Patient number 417 did however receive the 50% rescue dose.

The number of patients reporting an event during the double-blind phase and the number of events in each treatment group are summarised in Table 61 below:

Table 61. Summary of adverse events reported during the double-blind phase

	Treatment group			
	Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Number of patients reporting an adverse event	42 (62%)	42 (59%)	45 (67%)	38 (58%)
Number of events reported	83	97	102	76

The severity and relationship to therapy of adverse events reported during the double-blind phase are summarised in Table 62 below:

Table 62. Summary of severity and relationship to therapy during the double-blind phase

		No of reports (%)			
		Treatment group			
		Hyd. 2 mg	Hyd. 4 mg	Hyd. 6 mg	Morphine 20 mg
Severity	Mild	60 (72%)	68 (70%)	75 (74%)	49 (64%)
	Moderate	22 (27%)	23 (24%)	20 (20%)	21 (28%)
	Severe	1 (1%)	6 (6%)	7 (7%)	5 (7%)
	Unknown	-	-	-	1 (1%)
Relationship to therapy	Definite	-	1 (1%)	-	-
	Probable	8 (10%)	9 (9%)	11 (11%)	8 (11%)
	Possible	40 (48%)	50 (52%)	53 (52%)	31 (41%)
	Unlikely	24 (29%)	20 (21%)	27 (26%)	18 (24%)
	None	7 (8%)	17 (18%)	11 (11%)	19 (25%)
	Unknown	4 (5%)	-	-	-

The most commonly reported events (i.e. reported by more than 5% of patients in any treatment group) are summarised in Table 63 below:

Table 63. Summary of adverse events reported by >5% of patients in any treatment group during double-blind phase

MedDRA preferred term	Number of patients reporting			
	Treatment group			
	Hyd. 2 mg (n=68)	Hyd. 4 mg (n=71)	Hyd. 6 mg (n=67)	Morphine 20 mg (n=65)
NAUSEA	29 (43%)	30 (42%)	28 (42%)	19 (29%)
VOMITING	3 (4%)	10 (14%)	11 (16%)	7 (11%)
PYREXIA	4 (6%)	6 (8%)	9 (13%)	6 (9%)
SEDATION	6 (9%)	3 (4%)	4 (6%)	2 (3%)
HEADACHE	5 (7%)	2 (3%)	3 (4%)	1 (2%)
CONFUSION	-	4 (6%)	3 (4%)	1 (2%)
ANAEMIA	1 (1%)	-	4 (6%)	1 (2%)

Nausea was more commonly reported on hydromorphone treatment. A total of 87 (42%) patients treated with hydromorphone reported nausea compared to 19 (29%) patients in the

morphine sulphate 20 mg treatment group. Generally, the reports of nausea, vomiting and sedation were assessed by the investigator as being probably or possibly related to treatment, whilst reports of pyrexia were assessed as having an unlikely or no relationship to treatment. The difference between treatment groups in the proportion of patients reporting adverse events during the double-blind phase was not statistically significant (p=0.72).

Table 64 below lists the number of patients who had the commonly reported side effects associated with morphine (Moulin 1996) ongoing or starting during the double-blind phase. Therefore, this table includes patients who had ongoing adverse events at the time of randomisation which were not attributable to treatment.

Table 64. Summary of adverse events commonly reported with morphine, ongoing or starting during double-blind phase (Moulin 1996)

MedDRA preferred term	Number of patients reporting (%)			
	Treatment group			
	Hyd. 2 mg (n=68)	Hyd. 4 mg (n=71)	Hyd. 6 mg (n=67)	Morphine 20 mg (n=65)
VISION BLURRED	-	-	-	1 (2%)
ABDOMINAL PAIN	1 (1%)	-	-	-
ABDOMINAL PAIN UPPER	-	1 (1%)	1 (1%)	-
CONSTIPATION	2 (3%)	2 (3%)	5 (7%)	3 (5%)
DRY THROAT	-	-	-	1 (2%)
NAUSEA	30 (44%)	35 (49%)	29 (43%)	22 (34%)
VOMITING	3 (4%)	13 (18%)	12 (18%)	7 (11%)
MALAISE	-	-	1 (1%)	-
DIZZINESS (EXC VERTIGO)	1 (1%)	1 (1%)	-	1 (2%)
SEDATION	6 (9%)	4 (6%)	4 (6%)	3 (5%)
SOMNOLENCE	-	1 (1%)	1 (1%)	1 (2%)
CONFUSION	-	4 (6%)	3 (4%)	1 (2%)
SLEEPING DISORDER	1 (1%)	1 (1%)	-	-
PRURITUS	1 (1%)	2 (3%)	1 (1%)	-
Number of patients reporting any of the above	37 (54%)	43 (61%)	40 (60%)	27 (42%)

Five patients reported serious adverse events during the double-blind phase. Three of these patients (hydromorphone 4 mg: patient number 461, hydromorphone 6 mg: patient number 41, morphine sulphate 20 mg: patient number 12) were withdrawn from the study as a consequence of their serious adverse events. Another patient (number 449, hydromorphone 2 mg) subsequently withdrew his consent. In addition, all the events resolved, all were of either moderate or severe severity and all those experienced by patients treated with hydromorphone were considered to have an unlikely or no relationship to therapy by the investigator. There were no deaths during the study.

Patient number 449 (hydromorphone 2 mg) experienced pain in the abdomen/stomach. Subsequently, he withdrew his consent to participate in the study after 24 hours of the double-blind phase. Cholecystitis was diagnosed and the patient underwent a cholecystectomy operation. Patient number 461 (hydromorphone 4 mg) experienced a transient ischaemic attack and was transferred to an intensive care unit. Treatment with study medication was permanently stopped because of this adverse event after 1470 minutes of the randomised phase and the patient received symptomatic therapy. Patient number 41 (hydromorphone 6 mg) complained of chest pain upon deep inspiration. Arterial blood gases indicated poor oxygenation. A pulmonary embolism was diagnosed. The patient received symptomatic therapy and as a result of the adverse event was permanently withdrawn from the study after 1760 minutes of the randomised phase. Patient number 12 (morphine sulphate 20 mg) experienced dizziness, sweating, blurred vision, tachypnoea and had a blood pressure of 100/60 and a 70% decrease in oxygen saturation during physiotherapy. Both the sweating and blurred vision were considered to have a possible relationship to treatment by the investigator, whilst the dizziness and tachypnoea were considered to have an unlikely or no relationship to treatment, respectively. Atrial fibrillation was diagnosed and as a result he was permanently withdrawn from the study after 60 minutes of the randomised phase. Patient number 561 (morphine sulphate 20 mg) experienced increased heart rate, phlebitis and a pulmonary embolism. This adverse event was considered to have no relationship to therapy by the investigator. The patient underwent symptomatic therapy until the events resolved.

Table 65 presents the results of the analysis of the AUC (0-48 hours) of respiration rate/48 for the observed data. For this analysis, the actual adjusted means (breaths/min) were 17.6 (hydromorphone 2 mg), 17.6 (hydromorphone 4 mg), 17.3 (hydromorphone 6 mg) and 17.4 (morphine sulphate 20 mg). In the analysis of covariance the term for treatment group was not statistically significant (p=0.80).

Table 65. Analysis of covariance for the AUC (0-48h) of respiration rate/48 (observed data)

AUC (0-48h) for respiration rate/48[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Mean	17.6	17.4	17.5	17.6
sd	2.8	2.9	3.2	2.6
Range	12.2, 25.5	11.2, 26.7	12.3, 25.7	13.0, 25.7
Adjusted mean[b]	17.6	17.6	17.3	17.4
Difference in adjusted means relative to morphine 20mg[c]	0.3	0.2	-0.1	
se (of difference)	0.4	0.4	0.4	
98.3% CI for difference[d]	-0.7, 1.2	-0.7, 1.2	-1.0, 0.9	

Analysis of covariance	F	df	p
Baseline	95.87	1, 264	<0.001
Treatment group	0.33	3, 264	0.80
Country	14.04	2, 264	<0.001

a The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original recorded values
b Adjusted for baseline and country
c A negative difference favours hydromorphone
d Sidak adjusted 95% CI

Table 66 presents the results of the analysis of the AUC (0-48 hours) of level of sedation/48 for the observed data. For this analysis, the actual adjusted means were 0.19 (hydromorphone 2 mg), 0.23 (hydromorphone 4 mg), 0.25 (hydromorphone 6 mg) and 0.26 (morphine sulphate 20 mg). In the analysis of covariance the term for treatment group was not statistically significant (p=0.23).

Table 66. Analysis of covariance for the AUC (0-48h) of level of sedation/48 (observed data)

AUC (0-48h) for level of sedation/48[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Mean	0.19	0.23	0.24	0.26
sd	0.20	0.20	0.22	0.25
Range	0.00, 0.93	0.00, 0.84	0.00, 0.96	0.00, 0.95
Adjusted mean[b]	0.19	0.23	0.25	0.26
Difference in adjusted means relative to morphine 20mg[c]	-0.07	-0.03	-0.01	
se (of difference)	0.04	0.04	0.04	
98.3% CI for difference[d]	-0.16, 0.02	-0.12, 0.06	-0.10, 0.08	

Analysis of covariance	F	df	p
Baseline	2.95	1, 264	0.09
Treatment group	1.46	3, 264	0.23
Country	0.18	2, 264	0.83

a The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = awake, alert, orientated; 1 = dozing intermittently, drowsy or lethargic but aroused by physical stimulus; 2 = mostly sleeping, difficult to arouse but feasible by physical stimulus; 3 = difficult to waken, little or no response even to physical stimulus)
b Adjusted for baseline and country
c A negative difference favours hydromorphone
d Sidak adjusted 95% CI

Table 67 presents the results of the analysis of the AUC (0-48 hours) of degree of nausea/48 for the observed data. For this analysis, the actual adjusted means were 0.10 (hydromorphone 2 mg), 0.12 (hydromorphone 4 mg), 0.07 (hydromorphone 6 mg) and 0.05 (morphine sulphate 20 mg). In the analysis of covariance the term for treatment group was not statistically significant (p=0.15). Although there were trends for more nausea in the three hydromorphone treatment groups, all three Sidak-adjusted 95% confidence intervals contained zero, implying that the pairwise comparison for each of the three doses against morphine sulphate 20 mg were not statistically significant at the 1.7% level.

Table 67. Analysis of covariance for the AUC (0-48h) of degree of nausea/48 (observed data)

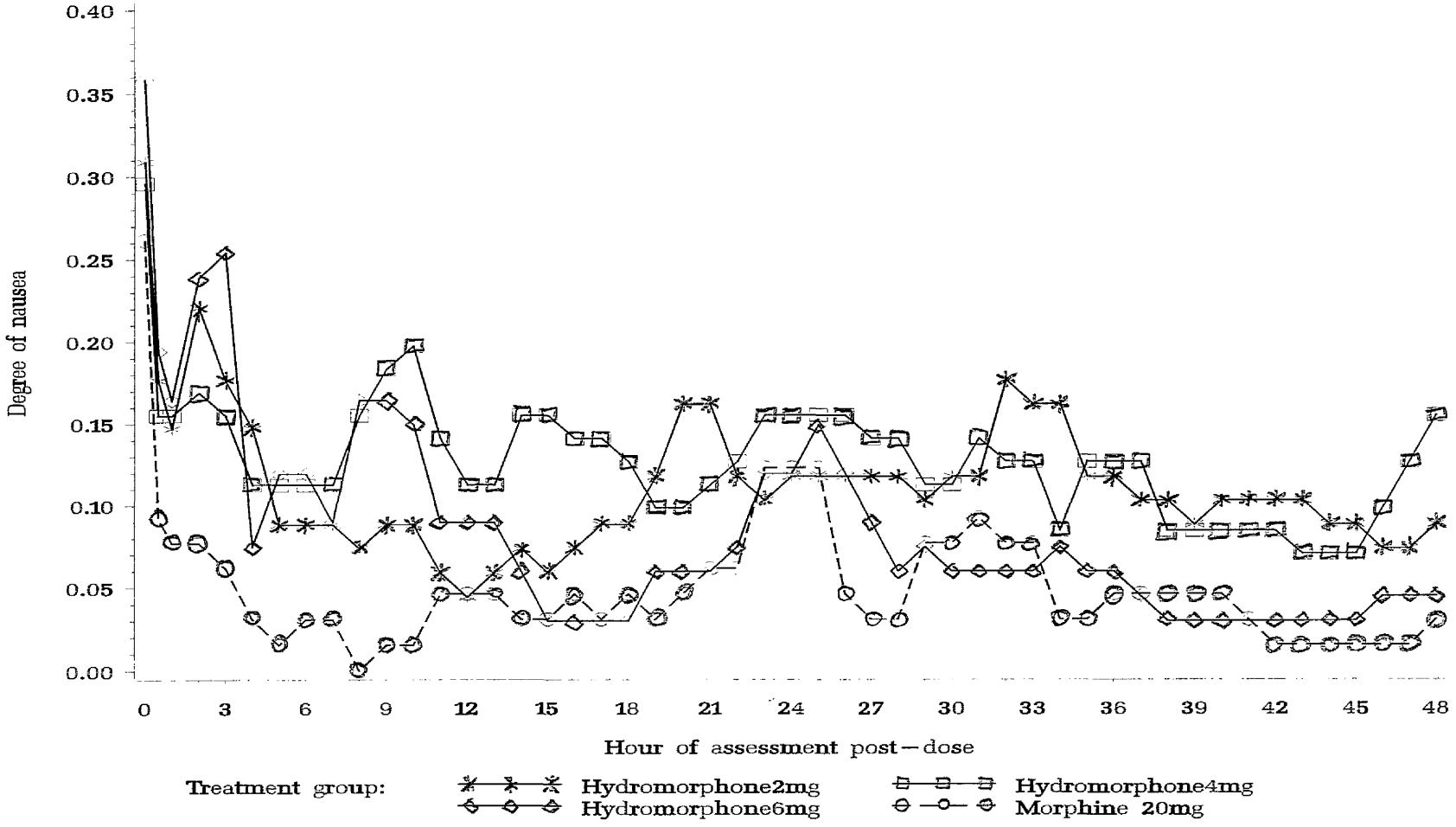
AUC (0-48h) for degree of nausea/48[a]	Treatment group			
	Hydromorphone 2 mg	Hydromorphone 4 mg	Hydromorphone 6 mg	Morphine 20 mg
Total number of patients	68	71	67	65
Mean	0.11	0.13	0.08	0.05
sd	0.29	0.22	0.18	0.12
Range	0.00, 1.78	0.00, 0.95	0.00, 1.00	0.00, 0.71
Adjusted mean[b]	0.10	0.12	0.07	0.05
Difference in adjusted means relative to morphine 20mg[c]	0.06	0.08	0.03	
se (of difference)	0.04	0.04	0.04	
98.3% CI for difference[d]	-0.03, 0.15	-0.01, 0.16	-0.06, 0.11	

Analysis of covariance	F	df	p
Baseline	7.98	1, 264	0.005
Treatment group	1.79	3, 264	0.15
Country	3.14	2, 264	0.045

a The reason for dividing the AUC by 48 was so the value could be easily interpreted with the original scale (0 = none; 1 = mild; 2 = moderate; 3 = severe)
b Adjusted for baseline and country
c A negative difference favours hydromorphone
d Sidak adjusted 95% CI

As shown in Figure 18, the degree of nausea reported was less in the morphine sulphate 20-mg treatment group, particularly during the early stages of the double-blind phase.

Figure 18. Mean profile for degree of nausea (observed set – last observation carried forward)



Two (3%), 12 (17%) and 11 (16%) patients in the hydromorphone 2 mg, 4 mg and 6 mg treatment groups, respectively, recorded occurrences of vomiting during the double-blind phase compared to seven (11%) patients who received morphine sulphate 20 mg (Table 68). These data slightly contradict the data presented in Table 63 as this data was recorded in a separate section of the CRF to that of adverse events.

Table 68. Number of occurrences of vomiting reported during double-blind phase (observed data)

Treatment group	Number of occurrences of vomiting							Difference relative to morphine 20 mg	98.3% CI for difference[a]
	n	0	1	2	3	4	% not reporting any vomiting		
Hydromorphone 2 mg	68	66	2	-	-	-	97%	8%	-3%,18%
Hydromorphone 4 mg	71	59	8	3	1	-	83%	-6%	-20%,8%
Hydromorphone 6 mg	67	56	7	3	1	-	84%	-6%	-20%,9%
Morphine 20 mg	65	58	4	2	-	1	89%		

a Sidak adjusted 95% CI

The tolerability of the three hydromorphone doses in this study is comparable with that from 20 mg of morphine. The pattern of events of the treatments is typical of strong opioids, with additional events, such as pyrexia, being a feature of the postoperative setting. Some of the event rates are suggestive of trends, but statistical testing of these differences failed to demonstrate significance. This is typical of the need for far larger patient numbers to detect differences in adverse event profiles compared with numbers needed for efficacy assessment (McQuay 1998, Edwards 1999).

5.3.6 Discussion

One of the elements that was not controlled by the study, as in the case of the single-dose study also, was the anaesthetic procedure itself. The variability in anaesthetic technique resulted in some patients receiving regional anaesthetic procedures which could have long durations of action. General anaesthetics were much more commonly used in study centres in the UK and Eire compared to the centres in mainland Europe. Conversely, study centres in France and the Netherlands commonly used regional anaesthetics. These same data were not collected in the single-dose study, but it is likely that if they had been collected, the findings would have been the same, since many centres participated in both studies. However, the minimum of 18 hours from the patient leaving the operating theatre to the time of randomisation should have allowed for the effects of regional procedures to diminish to negligible levels. Investigators were instructed to confirm this by testing motor function in the affected limb.

The original sample size for the study was estimated to be 50 patients per treatment group. This assumed variability of 2.0 for the principal measure, 90% power, a true difference of zero between hydromorphone 4 mg and morphine sulphate 20 mg and a difference of 0.25 in favour of hydromorphone 6 mg over morphine sulphate 20 mg. After 52 patients completed the study the variability for the principal measure was re-estimated to be 2.24. Using this revised variability and 90% power, and assuming a true difference of zero between hydromorphone 4 mg and morphine sulphate 20 mg and a difference of 0.25 in favour of hydromorphone over morphine sulphate 20 mg, it was determined that 60 evaluable patients per treatment group were required. Subsequently, it was concluded that the study precision was adequate to meet its objectives; the revised sample size estimate of variability was 2.24, whilst the actual variability for the principal measure was 2.16 for the "full analysis" set and 1.92 for the per-protocol set.

According to the protocol, treatment with hydromorphone 2, 4 and 6 mg was to be considered equivalent to morphine sulphate 20 mg if the two one-sided tests for non-inferiority and non-superiority from the analysis of the AUC (0-48 hour) of pain at rest/48 for the "full analysis" set were significant at the 2.5% level. Results from the analysis showed this, and it was concluded that that the means for all three hydromorphone treatment groups were within ± 1.5 of the mean for morphine sulphate 20 mg. The actual adjusted means for the four treatments were 4.6 (hydromorphone 2 mg), 4.0 (hydromorphone 4 mg), 3.5 (hydromorphone 6 mg) and 3.9 (morphine sulphate 20 mg). The results also imply an ordering between the treatments, with hydromorphone 6 mg as the most effective treatment, hydromorphone 2 mg as the least effective treatment and hydromorphone 4 mg and morphine sulphate 20 mg being very similar. From these data, we can conclude that the equipotency ratio for morphine:hyhromorphone in this setting is between 4 to 5.

The equivalence zone (or "delta") that was used for the study was ± 1.5 on the 11-point pain scale from the Brief Pain Inventory. The selection of 1.5 as the value was based on consultation with clinical experts in pain management but it was not possible to validate this with any precise data. The same value has been presented as a clinically significant change on an 11-point scale in published papers and abstracts (Rowbotham 1998, Stubhaug 2000). Conversely, various recommendations exist for setting delta, such as half of the difference between active and placebo, 10% of the rating scale or half the standard deviation of the

measure at baseline. One possible approach to identifying what is a clinically significant change in pain scores is to look at the change following patients' discontinuation from the study. The majority of patients discontinuing from the randomised phase of the study were likely to be suffering inadequate analgesia. Following discontinuation, the investigators were at liberty to select analgesia to bring about control of the patients' pain. The consequent mean reduction in pain-at-rest scores through this process was approximately 3 points on the scale.

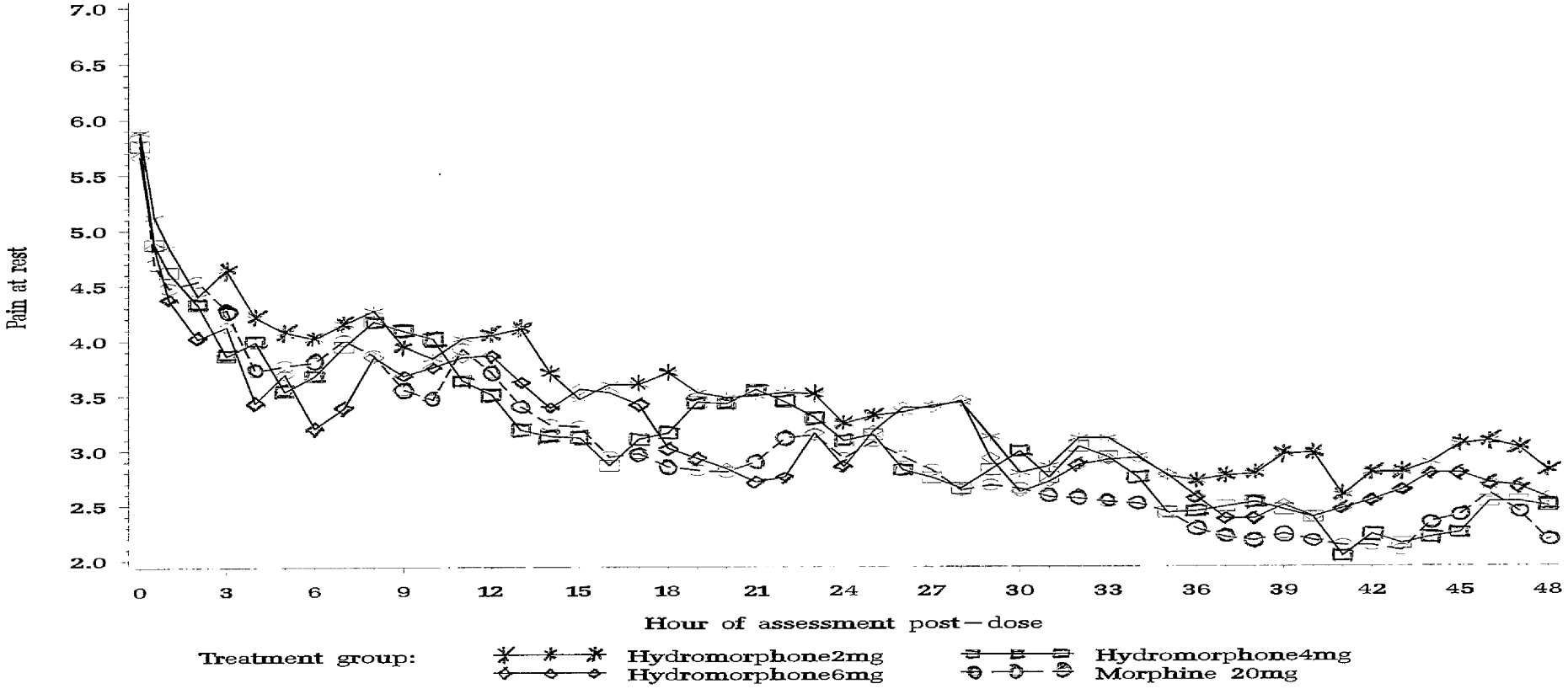
Because this was an equivalence study, it is argued by some that using the per-protocol set of patients to ascertain equivalence is more relevant than using the "full analysis" set. The per-protocol set excludes patients who withdrew during the first three hours after the first dose of study medication. The logic for excluding these patients is that as the study was a multiple-dose comparison over 48 hours, the inclusion of patients with little data and only one dose is somewhat irrelevant. Also the number of patients who withdrew "early" (i.e. at any point up to 3 hours post first dose) were reasonably similar in each of the four treatment groups: seven patients (10%) in the hydromorphone 2 mg treatment group, four patients (6%) in the hydromorphone 4 mg treatment group, three patients (4%) in the hydromorphone 6 mg treatment group and six patients (9%) in the morphine sulphate 20 mg treatment group. Therefore, removing early dropouts would be unlikely to bias the analysis in favour of a particular treatment. As a result of excluding these twenty patients the variability was less and therefore the confidence intervals were narrower. This was because patients who withdrew early generally had higher pain scores and as the analysis used was last-observation-carried-forward, this resulted in their having higher AUC values. Although the treatment group means were much closer together, the treatment group ordering remained the same as for the "full analysis" set. Based on these data, non-inferiority of each hydromorphone dose against morphine could have been inferred using a limit of 0.9 rather than the 1.5 quoted in the study protocol. For the per-protocol analysis, the actual adjusted means for the four treatments were 3.9 (hydromorphone 2 mg), 3.8 (hydromorphone 4 mg) 3.4 (hydromorphone 6 mg) and 3.8 (morphine sulphate 20 mg).

Because the primary efficacy endpoint pain score is based on a relatively long time period (48 hours), the question of how to handle patients dropping out of the study has to be considered. In this study, it was elected to use last-value-carried-forward (LOCF [Gillings 1991]) to allow inclusion of data from patients who withdrew prior to the 48-hour time

point. This is one of the accepted methods of assessing such patients in studies in analgesia, and it provides a conservative estimate of efficacy. This is because patients who withdrew due to poor efficacy would have a high pain score at the time of discontinuation and this high score will be carried forward for the remainder of the 48-hour period, for the purposes of analysis. Separate analyses were conducted to test the effect of this carryforward method and they validated this approach.

As part of the protocol specifications, pain at rest data was recorded up to 48 hours for all patients irrespective of whether they had withdrawn. Graphical illustration of this data (Figure 19), shows the effect of the use of rescue analgesia and indicates that the mean profiles for each treatment group were very similar.

Figure 19. Mean profile for pain at rest ("full analysis" set but also including assessments subsequent to withdrawal)



Although the data for the number and total dosage of study medication taken seemed fairly consistent across treatment groups, there was some evidence to suggest that patients in the hydromorphone 2 mg treatment group were taking more study medication per unit time than the other three treatment groups. Assuming a dosing interval of 4.5 hours (midway between the protocol defined dosing interval of 3 to 6 hours), the median dose per 4.5 hours could be calculated and referred back to the original randomised dose. For the hydromorphone 2-mg treatment group, the median dose per 4.5 hours was 1.8 mg (90% of the randomised 2-mg dose). The equivalent values for the other treatment groups were 2.61 mg (65%) for the hydromorphone 4 mg treatment group, 4.23 mg (71%) for the hydromorphone 6 mg treatment group and 13.14 mg (66%) for the morphine sulphate 20 mg treatment group. From these data, we can conclude that patients in the hydromorphone 2-mg treatment group did in fact take a greater percentage of the randomised dose in order to remain in the study. Furthermore, when analysing the average time between doses it can be shown that the median time was shorter in the hydromorphone 2 mg treatment group, namely 5.6 hours compared to the other three treatment groups: 6.6 hours in the hydromorphone 4 mg treatment group, 6.4 hours in the hydromorphone 6 mg treatment group and 7.0 hours in the morphine sulphate 20 mg treatment group.

Results were similar for the analyses of pain on movement: actual adjusted mean values for AUC (0-48 hours) of pain on movement/48 for the "full analysis" set were 6.6 for the hydromorphone 2 mg treatment group, 6.1 for the hydromorphone 4 mg treatment group, 5.7 for the hydromorphone 6 mg treatment group and 5.8 for the morphine sulphate 20 mg treatment group. As expected mean AUC pain on movement scores were higher than the pain at rest scores.

The mean pain at rest scores at baseline in this study were much higher (5.8), than in the earlier single-dose clinical study, where the value was 4.4. This arose as a result of one of the inclusion criteria in the current study which stated that patients entered into the study were to have pain at rest scores of at least 4 at randomisation. After randomisation, mean pain scores remained higher than in the earlier study, for the first three hours. After this point mean pain levels were lower than in the earlier study, as the multiple dose aspect of the study started having an effect.

For the analysis of AUC (0-48 hours) pain at rest/48 for the "full analysis" set, there was an ordering of the responses within the three hydromorphone randomised groups. The adjusted means were 4.6 (hydromorphone 2 mg), 4.0 (hydromorphone 4 mg) and 3.5 (hydromorphone 6 mg). The mean difference of 1.1 (98.3% CI 0.1,2.0) between the hydromorphone 6 mg and 2 mg groups, was statistically significant, indicating that there was evidence of increasing efficacy between the three hydromorphone doses. Although the actual difference of 1.1 was in the protocol defined equivalence region, the upper bound of the confidence interval implies that the superiority of the hydromorphone 6-mg dose over the hydromorphone 2-mg dose cannot be discounted. Furthermore as discussed previously, there was some evidence that patients in the hydromorphone 2-mg group were taking more medication than the patients in the other two hydromorphone groups. This implies that the true difference between the 2-mg and 6 mg groups was in fact slightly larger.

As in the single-dose study, a high proportion of patients withdrew from this study. In total, 99 (37%) patients withdrew from the study (the withdrawal rate in the single-dose study was also 37%). This included 47 patients (17%) who withdrew because of lack of efficacy, although, as referred to earlier (see Section 5.3.5), the different categories overlap to a large degree. Completion rates in the respective countries varied (79% in France, 64% in the UK and Eire, and 52% in the Netherlands). Within countries, there were marked differences between centres in respect to the percentage of patients completing the study period. Within each centre, however, the completion rate did not vary greatly between the study treatments. This suggests that the variability was due to investigator technique, rather than treatment-related factors. More patients withdrew from the hydromorphone 2-mg treatment group. Seventy-eight out of the 99 (79%) patients who withdrew from the study used rescue medication other than the 50% "rescue" dose. Morphine was the most commonly used rescue medication, being administered in 48 (62%) patients. The proportion of patients receiving morphine as rescue medication was similar across the dose groups. There were no statistically significant differences between the treatment groups for the time to withdrawal.

The safety profile of hydromorphone was good. There was no statistically significant difference between the four treatment groups in the proportion of patients reporting adverse events. Most adverse events were mild and the relationship to therapy was unlikely or none for approximately 40% of the reported events. Nausea, vomiting, pyrexia and sedation were the most common adverse events. Generally, the reports of nausea, vomiting and sedation

were assessed by the investigator as being probably or possibly related to treatment, whilst the reports of pyrexia were assessed as having an unlikely or no relationship to treatment. This is not unexpected as nausea, vomiting and sedation are commonly reported side effects associated with opioids at the start of treatment, which usually resolve within a few days (O'Neill 1997). Some of the event rates are suggestive of trends, but statistical testing of these differences failed to demonstrate significance. This is typical of the need for far larger patient numbers to detect differences in adverse event profiles compared with numbers needed for efficacy assessment (McQuay 1998). One factor that could have affected the relative incidence of adverse events is the way in which all patients were stabilised on morphine (PCA) and then either continued on morphine orally, or switched to hydromorphone. Patients are not thought to react equally to all opioids, even those of similar receptor affinity (Bruera 1996). It is possible that during the morphine PCA phase, patients who responded well to morphine were selected out of the total patient population, thus selecting a subset of patients who would be more likely to obtain good efficacy and tolerability from morphine than hydromorphone. Another possibility was that patients became tolerant to the side effects of morphine during the PCA phase of the study. Subsequently during the double-blind phase of the study, patients treated with hydromorphone had to become re-acclimatised to their opioid treatment whereas those randomised to receive morphine did not.

A total of 14 patients withdrew from the study due to adverse events (three in the hydromorphone 2-mg treatment group, five in the hydromorphone 4-mg treatment group, five in the hydromorphone 6-mg treatment group and one in the morphine sulphate 20-mg treatment group). The serious adverse events reported during the double-blind phase of the study were all considered to have an unlikely or no relationship to study medication by the investigator. There were no clinically significant differences in respiratory rate, level of sedation or nausea and vomiting gradings between the four treatment groups.

5.3.7 Conclusions

Hydromorphone 2mg, 4mg and 6mg were considered equivalent to morphine 20mg in the treatment of pain in the post-operative recovery of patients who underwent primary knee replacement surgery. Efficacy increased with increasing doses, the 6-mg dose being statistically significantly more potent than the 2-mg dose. The 4-mg dose was closest in

efficacy to the morphine sulphate 20-mg dose, suggesting an equipotency ratio of 5 for this setting. The tolerability of the three hydromorphone doses was comparable to morphine sulphate 20 mg. These findings confirm impressions gained from more than 50 years of clinical use in North America. Namely, hydromorphone is an effective and safe analgesic in the treatment of acute pain.

The results of this study were given as an oral presentation at the European Congress of Anaesthesiology in Florence, Italy, June 2001. The presenting author was Dr Slappendel. (Slappendel 2001b).

5.4 Active-controlled study in cancer pain

5.4 Active-controlled study in cancer pain

5.4.1 Study summary

The title of the study was "A randomised, double blind, controlled study of hydromorphone (immediate and controlled-release) versus morphine (immediate and controlled-release) in cancer pain". The co-ordinating investigator was Dr Magdi Hanna, Director of the Analgesics & Pain Relief Research Unit, King's College of Medicine and Dentistry, Bessemer Road, London SE5 9RS.

The primary objective was to demonstrate the clinical equivalence of efficacy between hydromorphone [immediate- (IR) and controlled-release (CR)] and morphine (IR and CR). Equivalence of efficacy was assessed using the "worst pain" item of the Brief Pain Inventory (BPI). Secondary objectives included a comparison of the following variables between hydromorphone and morphine: other assessments of pain from the BPI; number of breakthrough pain medication doses taken; time to dose stabilisation during both IR and CR phases of the study; number of patients dropping out during each phase; number of patients changing dose level during the CR phase; mean number of dose level changes during the CR phase; safety and tolerability.

The methodology was of a multicentre, double blind, randomised, active-controlled, multiple-ascending-dose study to evaluate the clinical equivalence and tolerability of an IR and CR formulation of hydromorphone and morphine in patients with cancer pain. Study medication was titrated for each patient until pain control was achieved; patients received hydromorphone 12 to 108 mg/day or morphine 60 to 540 mg/day for up to 24 days (the IR formulations were given for 2 to 9 days and the CR formulations for 10 to 15 days). Assessments of pain were made at intervals throughout the study.

Two hundred patients were randomised and received study medication: 77/99 (78%) patients completed the hydromorphone IR phase and 86/101 (85%) completed the morphine IR phase. For the CR phase, 60/77 (78%) patients completed in the hydromorphone group and 73/86 (85%) in the morphine group. Data for 190 patients were included in the analysis of the primary variable for the IR phase and for 157 patients in the CR phase.

The diagnostic criteria were; inpatients, outpatients or day patients ≥18 years of age, who had cancer pain suitable for treatment with once-daily strong opioid analgesics and who required between 60 to 540 mg of oral morphine or equivalent every 24 hours for up to 24 days.

The measures of efficacy were Brief Pain Inventory, number of breakthrough pain medication doses, time to dose stabilisation in IR and CR phases, number of patients who dropped out during each phase, number of patients who changed dose level in CR phase, mean number of dose level changes in CR phase. The measures of safety were adverse events.

The results of the study showed that there were decreases in "worst pain" in both treatment groups, confirming the basic efficacy of the two treatments under the study conditions. According to the protocol, treatment with hydromorphone was to be considered equivalent to morphine if the 95% two-sided confidence interval for the difference between the adjusted means for the principal measure of efficacy ("worst pain" score of BPI in the past 24 hours) lay within -1.5 to 1.5. For the IR phase this was true and therefore hydromorphone IR was proven to be equivalent to morphine IR (mean difference of 0.2, 95% CI –0.4 to 0.9). For the CR phase the lower limit of the 95% confidence interval was less than –1.5 which implied that the superiority of hydromorphone could not be disproved. However, the upper limit was less than 1.5 and therefore non-inferiority of hydromorphone was proven. Furthermore, there was a statistically significant difference between the treatment groups in favour of hydromorphone for the CR phase for both the "per protocol" and the "full analysis" sets (mean difference of -0.8, 95% CI –1.6 to –0.01, p=0.046).

The dose levels at which patients reached dose stable pain control were similar in the two treatment groups, suggesting that the packaging of the six dose levels of the respective treatments was well matched.

For the secondary efficacy variables (other BPI variables) there were no statistically significant differences between the treatments. There was also a trend in favour of hydromorphone for "pain now" p.m. at the end of CR phase (p=0.09).

Although the use of breakthrough pain medication was statistically significantly higher for the hydromorphone group in the IR phase, by the end of the CR phase there was no difference between the two treatment groups, again suggesting equivalence of the two therapies. The number of patients having dose level changes during the CR phase was similar in both treatment groups.

The overall safety profiles of the two treatments were generally similar and there were no statistically significant differences between the treatments for the proportion of patients reporting adverse events. Overall, irrespective of study phase, 80/99 (81%) hydromorphone-treated patients reported 347 adverse events compared to 90/101 (89%) patients in the morphine treatment group who reported 355 adverse events.

The nature of the adverse events reported during hydromorphone and morphine therapy was generally typical of the events associated with these treatments. Most of the adverse events in the study were mild or moderate in severity and around half were recorded as being of unlikely or no relationship to therapy. The higher number of withdrawals in the hydromorphone group in the CR phase of the study (22%) compared to morphine (15%) is difficult to explain but was not statistically significant. There was no statistically significant difference between treatment groups in the time to withdraw, irrespective of phase ($p=0.17$).

The occurrence of three deaths during the study, together with a further 17 patients who experienced serious adverse events was not unexpected, given the severity of the patients' conditions and the progressive nature of the disease. None of the deaths were considered to be related to the study therapy. Many of the serious adverse events tended to be associated with the underlying disease, although a proportion (32%) were considered to be definitely or probably related to the study treatment.

In conclusion, despite the complexity of the setting for this study, including the need for dose titration and the need for use of breakthrough pain medication, the results of this study clearly demonstrated equivalence for "worst pain" between hydromorphone IR and morphine IR. For the CR treatments, the superiority of hydromorphone to morphine could not be disproved; however, non-inferiority of hydromorphone to morphine was proven and there were statistically significant differences in favour of hydromorphone for the CR phase. The safety profiles of the two treatments were comparable with a numerical advantage for

hydromorphone CR which was not statistically significant. Overall, hydromorphone CR provides a convenient, once-daily treatment for cancer pain patients which offers superior pain control compared to twice-daily morphine.

5.4.2 Introduction

The first principle of managing cancer pain is an adequate and full assessment of the cause of the pain. With effective assessment and a systematic approach to the choice of analgesic agents, over 80% of cancer pain can be controlled with the use of orally self-administered drugs, used at regular intervals (O'Neill 1997). Opioid analgesic drugs, such as morphine, are the most common agents used in the management of cancer pain.

The aim of this study was to investigate whether, in the treatment of patients with cancer pain, hydromorphone IR and morphine IR were equivalent and whether the new once-daily CR formulation of hydromorphone was equivalent to twice-daily morphine CR. The study had to achieve these aims within the setting of the conventional management of cancer pain. This convention is that patients have their pain controlled using regular four-hourly doses of oral immediate-release medication, supplemented with identical doses of immediate-release medication for the purpose of treating "breakthrough pain". Monitoring the use of supplemental doses and the pain control achieved allows the regular four-hourly dose to be adjusted until an optimum balance is achieved between pain control and opioid-related side effects. Once this optimum dose has been determined, the total daily dose of the opioid is used to select a corresponding dose of a controlled-release opioid formulation. This allows less frequent dosing but should not compromise the pain control achieved by the patient. Supplemental dosing with immediate-release formulation continues when the patient is receiving regular controlled-release opioid for the same purpose as before, namely, the treatment of "breakthrough pain". As in the case with immediate-release regular dosing, the dose of the regular dose of controlled-release medication can be adjusted to achieve the optimum balance of pain control and side effects (O'Neill 1997).

The study was established as a multinational, predominantly European one. As such, the applicability of the treatment paradigm, as described above, had to be confirmed with investigators in candidate participating countries. The treatment paradigm was found to be acceptable in most cases, but not in Denmark, where there was a strong bias towards initial

treatment of the patient with a controlled-release formulation, avoiding the initial immediate-release treatment phase. This opinion also seemed prevalent in Germany, but not to the extent that it was not possible to carry the study out here. It was considered that in these specific countries, patients could go directly to the controlled-release phase of the study. However, this would have failed to meet the European regulatory agencies' demand for efficacy data for both the immediate-release and the controlled-release formulation of hydromorphone.

Morphine was selected as the comparator agent, since it is widely regarded as the "gold standard" in the treatment of cancer-related pain (WHO 1996a). For the controlled-release treatment phase of the study, there was a range of possible formulations to be used. Morphine twice daily (MS Contin, from Napp/Purdue-Frederick/Mundipharma) was selected, since it was the most widely accepted and also the most widely available agent in the countries participating in the study.

The duration of treatment was made as long as practicably possible, since in the setting of the treatment of chronic pain, a relatively long duration of treatment would be necessary to mimic the clinical setting. Two factors acted against this, however. The first was the patient population being studied. The relatively late-stage disease that was anticipated meant that patients would be relatively unstable and that there would even be some deaths within a few days or weeks of randomisation. The second factor was the bulk of the drug packaging required for double-blind titration to six dose-levels and the provision of two different formulations for each treatment. The packaging for the maximum of 24 days' treatment that was selected was the size of a small suitcase for each patient. Given that the test treatments are controlled drugs, the drug packaging had to be held within special cabinets at many centres. The bulk of the packaging therefore presented a real practical problem in the storage of patients' drug supplies.

The selection criteria were originally set in a fairly stringent manner to try and control for as many factors as possible affecting pain control in cancer pain patients. Unfortunately, this seemed to hinder recruitment. Additionally, from the data collected from the initial set of patients, it became clear that despite the controls in the protocol, the disease state itself (usually relatively late-stage cancer) meant that there were many other factors affecting pain control which it was impossible to control for. Therefore, given these two observations,

some restrictions on selection criteria were lifted relatively early in the study. These included factors such as concomitant chemotherapy and radiotherapy. From the final outcome of the study, it seems that this relaxation in selection criteria did not adversely affect the result.

The "worst pain" question in the Brief Pain Inventory was selected as the primary efficacy measure. It is one of a series of questions that a patient answers when they complete the inventory. The decision was based on;

a) The general acceptability of numerical rating scales as pain measures.
b) The "worst pain" measure in the Brief Pain Inventory is judged to be the most clinically significant measure (Daut 1983).
c) We were informed by the statistician with Dr Cleeland's group (from whom the BPI originated), Professor Tito Mendoza, that the "worst pain" measure was the most sensitive measure to use in a clinical study.
d) The availability of a validated translated version of the pain scale for the countries involved in the study. For the case of the Swedish and Flemish languages, we carried out specific validation studies to create a translated version (Mendoza 2001a.), but for all other languages, they were already available.

The general statistical approach to the study was one of seeking equivalence, rather than a difference from the comparator. This is a conventional approach in European registration studies where there is an established "gold standard" treatment and where the knowledge of the pharmacological and pharmaceutical details of the test product do not suggest the possibility of a clear advantage. The clinically significant zone of ± 1.5 was established through consultation with opinion leaders in the same way as described for the multiple-dose acute pain study (see section 5.3.6).

5.4.3 Objectives

The preplanned objectives of the study were:

- To demonstrate the clinical equivalence of efficacy between hydromorphone (immediate- and controlled-release) and morphine (immediate- and controlled-release). Equivalence of efficacy was assessed using the mean of the last two days of each treatment phase for the "worst pain" item of the Brief Pain Inventory (BPI) as reported by the patient.
- Other assessments from the BPI
- Number of breakthrough pain medication doses taken
- The time to dose stabilisation during both phases of the study
- The number of patients dropping out during each phase
- The number of patients having to change dose level during the controlled-release phase of the study
- The mean number of dose level changes during the controlled-release phase of the study
- Safety and tolerability

5.4.4 Methods

This was a multicentre, phase III, randomised, double blind, double dummy, active-controlled, parallel-group, multiple ascending dose, equivalence study comparing hydromorphone and morphine in the treatment of cancer pain. The study comprised two phases: an immediate-release (IR) phase during which patients received the IR medication (hydromorphone or morphine) and were titrated to pain control, followed by a controlled-release (CR) phase during which the patient received the CR formulation of the medication.

The study was conducted at 37 centres in the United Kingdom, Holland, Sweden, Belgium, France, Germany, Spain and Canada. The planned sample size was 140 patients, randomised equally to the hydromorphone or morphine treatment groups. The sample size was increased to 170 patients following the results of a planned, blinded interim analysis which was conducted after 55 patients had completed treatment. The purpose of the analysis was to re-estimate the variability of the primary variable. This analysis was repeated after

120 patients had completed the study and the sample size was increased further to 200 patients.

5.4.4.1 Patient selection

Individuals eligible for entry into this study comprised male or female inpatients, outpatients or day patients aged 18 years or older, who had cancer pain and were currently receiving strong oral or transdermal opioid analgesics, or for whom strong opioid analgesics were appropriate. Patients must have had pain suitable for treatment with a once-daily formulation, have required or been expected to require between 60 to 540 mg of oral morphine or morphine equivalent every 24 hours for the chronic management of cancer pain and been reasonably expected to achieve stable opioid requirements. These patients were to be able, in the opinion of the investigator, to comply fully with the study requirements, including completing the BPI, and to have given written informed consent before entry.

Individuals not eligible for this study comprised any of the following groups: patients with pain which was not considered to be potentially responsive to opioids; patients who only experienced pain on movement; patients with a requirement for other opioid analgesics (apart from study medication) after randomisation; patients with a recent (within the previous six months) or current history of drug and/or alcohol abuse; women of child bearing potential who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions; patients with intolerance of or hypersensitivity to hydromorphone (or other opioids); patients who were receiving or had received monoamine oxidase inhibitors (MAOIs) within the previous two weeks (Rossiter 1993); patients previously entered into this study; patients who had participated in another study with an investigational drug in the previous four weeks; patients with gastrointestinal disease of sufficient severity to be likely to interfere with orally administered analgesia including: dysphagia, vomiting, no bowel movement or bowel obstruction due to impaction within the five days prior to the start of the study, severe gut narrowing that may have affected the absorption or transit of orally administered drugs, particularly the insoluble OROS® outer coating; and patients in whom the risks of treatment with morphine/hydromorphone would have outweighed the potential benefits, including such risk categories as raised intracranial pressure, hypotension, hypothyroidism, asthma, reduced respiratory reserve, prostatic hypertrophy, hepatic impairment, renal impairment, elderly and debilitated, convulsive disorders and Addison's disease.

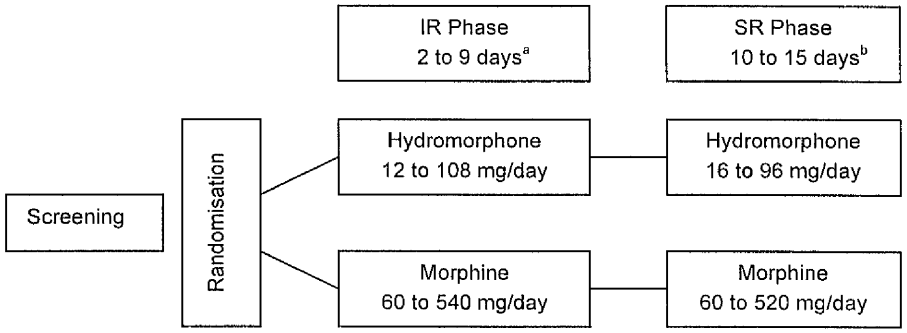
5.4.4.2 Study procedures

Patients were informed of the nature of the study and written informed consent for participation in the study was obtained prior to the performance of any study procedures. The patient was assessed for eligibility for the study according to the inclusion/exclusion criteria. Eligible patients were assigned a patient number which determined the medication they received during the study (hydromorphone or morphine). The baseline assessments included recording the patient's demographic data, fertility status, medical history and current status. Cancer diagnosis and the nature of predominant pain was recorded. A pregnancy test was performed, if applicable. Medication and non-drug therapy history were also recorded and a physical examination was performed, including the Mini-Mental State Examination and the Eastern Co-operative Oncology Group (ECOG) Performance Status Score. The ECOG Performance Status Score was recorded by the investigator at baseline and at the end of both the IR and CR phases. This measured the patient's level of activity and capability to care for themselves on a scale of zero to four, with four being the worst category (patient completely disabled, unable to carry on any self-care, totally confined to bed or chair). The patient completed the baseline patient diary assessments for the BPI, including "worst pain" in the past 24 hours and "pain now" ratings.

Opioids, other than study medication, were not allowed during the study. Monoamine oxidase inhibitors (MAOIs) were not allowed during the study nor within two weeks prior to entry. Adjuvant analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs, anxiolytics, antidepressants, antiarrhythmic drugs, hormone therapy, corticosteroids, anticonvulsants, and neuroleptics were allowed but had to be maintained at stable doses for the duration of the study. Adjuvant analgesics were not to be started during the study. Doses of other any other concomitant medications were to be kept constant during the study, when possible.

A diagram of the study design is given below:

Figure 20. Study design



[a]IR phase was complete when pain was controlled (≤3 requirements for breakthrough pain medication in the last 24 h) and dose stable (same dose level and no doses missed, except the 02.00 IR dose) for at least two consecutive days.

[b]CR phase was complete after a minimum of 10 days on CR medication if pain was controlled and dose stable for at least the previous two days.

5.4.4.2.1 Immediate-release (IR) phase

After completion of the baseline assessments, the investigator explained the use of the study and breakthrough pain medication. The IR phase medication was dispensed and the patient diary was given to the patient for completion during the study. During the IR phase, dose titration began with the dose level of the IR formulation which the investigator considered to be the most appropriate for the individual patient. Contact with the patient during the IR phase was daily, preferably by home or clinic visit but, if appropriate, by telephone. Any changes in concomitant medication and therapy and any adverse events were recorded. The patient was questioned regarding pain control, including the use of breakthrough pain medication and completion of the diary with details of medication taken and "worst pain" and "pain now" morning (a.m.) and evening (p.m.) ratings. The dose was up-titrated to the next dose level if the patient had more than three breakthrough pain episodes requiring breakthrough pain medication within the previous 24 hours. Doses could not be titrated more frequently than once a day. Dose titration was continued until dose stable pain control was achieved. Dose stable pain control was defined as being on the same dose level of study medication for a minimum of two consecutive days with no regular doses being missed (however, missing the 02.00 IR dose was permissible) and ≤3 requirements for breakthrough-pain medication in the previous 24 hours.

The duration of the IR phase was a minimum of two days and a maximum of nine days. For patients who had been using fentanyl patch analgesia, the IR phase was no shorter than seven days to allow a five-day washout from the effects of the patch.

When dose stable pain control had been achieved, contact was made by home or clinic visit and the end of the IR phase evaluation was carried out. The patient completed the diary, including the "worst pain" and "pain now" ratings from the BPI. The remaining questions on the BPI were completed by the investigator in consultation with the patient. The investigator recorded changes in concomitant medication and therapy and any adverse events. A physical examination was performed. The patient diary was collected and checked. Patients who achieved dose stable pain control entered the CR phase. Patients who did not achieve dose stable pain control by day nine were withdrawn from the study and the final evaluation was performed (as conducted on completion of the study).

5.4.4.2.2 Controlled-release phase

The investigator explained the use of the CR study medication and breakthrough pain medication and the CR medication was dispensed. The CR phase lasted a minimum of 10 days and a maximum of 15 days. Dosing in the CR phase, including dose level changes, always started with the morning dose. CR phase dosing began at the final IR dose level.

During this phase, each patient was contacted at least every three to four days, preferably by home or clinic visit but, if appropriate, by telephone. Changes in concomitant medication and therapy and any adverse events were recorded. The patient was questioned regarding the maintenance of pain control and completion of the diary. Up-titration to the next dose level occurred as in the IR phase (more than three breakthrough pain episodes requiring breakthrough pain medication within a 24-hour period), except that doses could be titrated only every second day. This was to allow for pharmacokinetic steady-state to be achieved for the controlled-release formulations (Shah 1997).

To complete the CR phase, patients must have achieved dose stable pain control for at least the final two days. The CR phase could be completed after day 10 if dose stable pain control had been achieved for at least the previous two days. Upon completion of the CR phase, contact was made by home or clinic visit for the final evaluation. The patient completed the

diary, including the "worst pain" and "pain now" ratings from the BPI and the remaining questions on the BPI were completed by the investigator in consultation with the patient. The investigator recorded changes in concomitant medication and therapy and any adverse events. A physical examination was performed including the Mini-Mental State Examination and the ECOG Performance Status Score. Patient diaries were collected and checked. At the end of the study period, patients were treated for their pain according to the local standard of practice or, where the particular centre had decided to take part in a follow-on study, the patient was offered hydromorphone CR with IR as breakthrough pain medication for the ongoing treatment of pain for a period of up to one year. The patient's treatment code was not broken at the time of moving on to the follow-on study. This follow-on study is currently in progress and will not be reported until 2002.

The methods of this study were presented at the European Association for Palliative Care congress in Berlin, in December 2000 (Hanna 2000) by Dr Hanna, the co-ordinating investigator for the study. The authors of this abstract were M Hanna, M Goulder (the project statistician) and the author, but due to uncertainties in the electronic abstract submission process, only Dr Hanna was listed as an author.

5.4.4.3 Study assessments

The schedule of efficacy and safety assessments made during the study is given below:

Table 69. Study schedule

Investigator assessment/procedure	Screening	Baseline	IR phase 2- 9 days Daily[a]	End of IR phase	CR phase 10-15 days Daily[b]	End of CR phase or at withdrawal[c]
Clinic or home visit	x	x	x or phone call	x	x or phone call	x
Inclusion/exclusion criteria	x	x				
Medical history		x				
Physical examination		x		x		x
ECOG Status		x				
Concomitant medication		x	x	x	x	x
Brief pain inventory		x		x		x
Dispense medication		x	as required	x	as required	
Dose titration			as required[d]		as required[e]	
Adverse events			x	x	x	x[f]
Final status						x
Patient assessment						
"Worst pain" in past 24 hours & "Pain now" (morning and evening)		x	x	x	x	x
Patient diary			x		x	

a: IR phase ended when patient achieved dose stable pain control for at least 2 consecutive days.
b: CR phase was complete after a minimum of 10 days on CR medication if pain was controlled and dose stable for at least the previous two days.
c: Assessment to be made on day last dose of medication taken
d: Doses were not to be titrated more frequently than once a day.
e: Doses were not to be titrated more frequently than every second day.
f: Contact was also to be made 3 days after last dose of study drug to determine patient's adverse event status

Patient's assessment of "worst pain" in the past 24 hours and "pain now" were recorded using the following 11-point numerical/descriptive rating scale taken from the Brief Pain Inventory:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Assessments of "worst pain" in the past 24 hours were scored by the patient, at baseline and once a day, every day, in the patient diary, just before taking the mid-morning dose of study medication. "Pain now" was scored by the patient, at baseline and twice a day, every day, in the patient diary, just before taking the mid-morning (a.m.) and evening (p.m.) doses, respectively.

The Brief Pain Inventory was completed by the investigator in consultation with the patient at baseline and at the end of the both IR and CR phases (with the exception of the "worst pain" and "pain now" sections, which the patient completed as described above). The variables recorded included: least pain in the past 24 hours and average pain (both measured on an 11-point scale); the percentage pain relief the treatment had provided; how pain had interfered with the following (each measured on an 11-point scale): general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life. Validated language versions of the Brief Pain Inventory were used in each respective country.

The date and time of use of breakthrough pain medication as well as the dose level and any changes in the dose level of study medication were recorded daily in the patient diary throughout the study.

All adverse events reported spontaneously by the patient or in response to questioning or observation by the investigator were recorded using the same categorisation as in the acute pain studies. Standard medical terminology was to be used according to the description published by Moulin (1996) for common opioid side effects and, where possible, a diagnosis was to be given rather than individual signs or symptoms. Changes in the severity of cancer pain were not reported as adverse events (unless they led to withdrawal from the study) since pain severity was recorded as part of the efficacy data. Adverse event data were collected from the start of study medication until three days after the last dose.

5.4.4.4 Study medication, blinding and randomisation

In the IR phase of the study, patients received either hydromorphone hydrochloride (HCl) 2, 4, 6, 8, 12 or 18 mg every four hours or morphine sulphate 10, 20, 30, 40, 60, or 90 mg every four hours. In the CR phase of the study, patients received either hydromorphone 16, 24, 32, 48, 72 or 96 mg every 24 hours or morphine sulphate 30, 60, 90, 120, 175, 260 mg every 12 hours. The doses were selected according to the available tablet strengths and a working equipotency value of 1:5. Dose titration began with the IR dose level which the investigator considered to be most appropriate for each individual patient.

In both the IR and CR phases, patients could also receive breakthrough pain medication: either hydromorphone or morphine sulphate, supplied as the IR formulation; a single dose

of breakthrough pain medication contained $^1/_6$ of the patient's daily dose in the IR phase and as close an approximation as was feasible in the CR phase. All study medication was administered orally.

For the IR formulations, all tablets were encapsulated in size 0 brown capsules. CR morphine sulphate and matching placebo were encapsulated in brown supro B capsules. CR hydromorphone and matching placebo were presented as tablets. Sufficient medication supplies were packed and labelled for 400 patients, including overage. Study medication at all dose levels, for both the IR and CR phases, as well as breakthrough medication, was packed in blister cards (colour coded for each dose level to aid dose level recognition) in containers with drug for 3 days' dosing. Medication was dispensed to suit individual patient dose requirements. The procedure for allocating medication was similar in both the IR and CR phases. The investigator started the patient at the desired dose level and the number of 3-day packs required was dispensed. In the IR phase this was up to three 3-day packs, giving enough supplies for 9 days at one dose level. In the CR phase this was up to five 3-day packs, giving enough supplies for 15 days at one dose level. The same number of packs of breakthrough pain medication, at the appropriate dose level, in both the IR and CR phases were also dispensed. Further medication was dispensed as required in cases of dose level changes.

Patients who met the study entry criteria were allocated a patient number in accordance with a central computer-generated randomisation list. Patients received numbers sequentially at each centre and the treatment they received was predetermined by the randomisation list. The patient number was identical to the treatment number pre-printed on the patient pack of medication.

Six dose levels were chosen for both IR and CR formulations as shown in the Tables 70 and 71. For the IR phase, the minimum dose of 10 mg morphine was chosen, as this was the smallest tablet size available. The lowest hydromorphone dose for this phase was matched to the morphine dose based on a 5:1 equipotency ratio. The number of dose steps was based on the likely requirements of the patients in this study setting of cancer pain. For the CR phase, it was not always possible to identically match the hydromorphone and morphine doses.

Table 70. Dose levels of IR morphine and hydromorphone

	Morphine	Hydromorphone
Dose level	Dose (mg) every 4h	Dose (mg) every 4h
1	10	2
2	20	4
3	30	6
4	40	8
5	60	12
6	90	18

Table 71. Dose levels of CR morphine and hydromorphone

	Morphine	Hydromorphone
Dose level	Dose (mg) every 12h	Dose (mg) every 24h
1	30	16
2	60	24
3	90	32
4	120	48
5	175	72
6	260	96

Dose titration began with the dose level of the IR formulation which the investigator considered to be most appropriate for each individual patient. The "oral morphine equivalent" of a previous opioid could be calculated using the following conversion factors as a guide:

Table 72. Oral morphine equivalent conversion table

Opioid	Conversion factor for oral morphine equivalent
Meperidine (pethidine)	x 0.2
Codeine	x 0.3
Hydrocodone	x 1.8
Oxycodone	x 2
Methadone	x 3
Hydromorphone	x 5
Levorphanol	x 15

For those patients who were already receiving opioid medication at entry to the study, the investigator was to consider incorporating a reduction in the dose conversion calculation to allow for incomplete cross-tolerance.

For all patients, the dose level could be increased in steps, missing none, until pain control was achieved (≤3 episodes of breakthrough pain in the last 24 hours). If more than 3 breakthrough pain episodes requiring breakthrough pain medication occurred within a 24-hour period, the investigator was to increase the dose to the next level. The dose level was not to be altered more frequently than once daily in the IR phase. It was recommended that patients consult with the investigator prior to changing to the next dose level.

To enter the CR phase of the study, patients must have had dose stable pain control for at least two consecutive days of the IR phase. The earliest a patient could have entered the CR

phase was on the morning of day 3 of the IR phase, provided that the dose was stable and the pain was controlled for the first two days.

In changing from the IR formulation to the CR formulation of the study medication, the patient was to be given the same dose level as their final IR formulation 24-hour dose. Thus, if a patient's pain was controlled on dose level 3 of the IR formulation, they were transferred to dose level 3 of the CR formulation. Dosing in the CR phase, including dose level changes, always started with the morning dose.

In the CR phase of the study, the dose level was adjusted as required, but only in single steps so that no dose level was skipped. The dose level was not to be altered more frequently than once every two days in the CR phase in order to allow steady-state drug levels to be reached.

The suggested IR phase dosing schedule was six times per day at 10.00, 14.00, 18.00, 22.00, 02.00 and 06.00 hours. The suggested CR phase dosing was twice per day at 10.00 and 22.00 hours (a double dummy technique was used to blind the hydromorphone once daily CR medication). In the IR phase the 02.00 hour dose could have been omitted completely, or omitted prospectively and a double dose given at 22.00 hours the previous day. Other dosing schedules were acceptable, if more convenient, provided that the dosing intervals of 4 and 12 hours in the IR and CR phases were strictly maintained and the doses were taken at the same time every day.

Regular dosing with study medication was to be done within one hour of the target time. In the IR phase, where dosing was delayed for greater than one hour, the delayed dose was to be taken as soon as possible. If the delay was as great as 4 hours, then a double dose was to be taken. Dosing delays of greater than 4 hours resulted in the delayed dose being missed. When dosing was delayed in the CR phase, the delayed dose was to be taken as soon as possible. Dosing delays of greater than 4 hours resulted in the delayed CR dose being missed completely and CR dosing re-commencing at the next scheduled time. During the intervening period patients were to use breakthrough pain medication as required to control pain.

All study medication (both capsules and tablets), was to be swallowed whole and not crushed, broken or chewed and was to be taken with fluid. The timing with respect to meals was not controlled.

This was a double blind, double-dummy study. Although the investigator and the patient were aware of the dose level being administered, both remained blind to the identity of the medication. The IR morphine and IR hydromorphone capsules were identical in appearance and were taken every 4 hours. However, the CR morphine was presented as a capsule to be taken every 12 hours and the CR hydromorphone was presented as a tablet to be taken every 24 hours. This was because of tablet sizes, it did not prove to be feasible to place the hydromorphone CR tablets inside a capsule. Thus, it was necessary to use placebo tablets and capsules in a double dummy technique in order the maintain blinding in the CR phase. Patients who received morphine CR twice daily were also given a placebo to match hydromorphone in the morning. Similarly, patients receiving hydromorphone CR once daily also received a placebo to match morphine in the morning and evening. Thus, both the patient and the investigator were unaware of the identity of the medication. Each participating centre had access to the treatment code for individual patients in the same way as described for the acute pain studies.

5.4.4.5 Data entry and statistical analysis

Data entry was performed in the same manner as that described for the acute pain studies. A random sample of 12 patients had all their information checked. The error rates were 0.01% for adverse events, 0.06% for withdrawal information, 0.06% for study medication and 0.02% for the principal measure of efficacy. The error rates were considered to be satisfactory and any discrepancies found were amended before analysis.

The statistical methods described in the protocol were expanded to produce a detailed statistical plan. This was discussed and agreed with the author and the Study Director, before the blind was broken and data made available for analysis. All statistical analyses were performed using the statistical analysis system SAS, release 6.12 under the Microsoft® Windows™ NT operating system (SAS Institute Inc 1990).

The two treatments were to be considered equivalent (for the immediate and controlled-release formulations separately), if the 95% two-sided confidence interval for the treatment difference fell wholly within the interval ±1.5. This interval was determined as being clinically relevant through consultation with opinion leaders in analgesia during the planning of the study. This difference was measured using the mean of the last two post-baseline recorded values (or last value, if only one value was available) for the "worst pain" score of BPI in the past 24 hours (principal measure of efficacy) in each respective treatment phase.

The "full analysis" set included all patients who took at least one dose of study medication and with at least one assessment performed within each of the respective phases of the study. Any patient with treatment administration errors was analysed according to the treatment actually taken. All efficacy variables were analysed using this set. For the principal measure of efficacy, the last two post-baseline recorded values at the end of each phase were used in the analysis (or last value, if only one value was available). This was to allow for the inclusion of patients who withdrew.

Because this was an equivalence study a per-protocol analysis was also performed. The per-protocol analysis set included all patients in the "full analysis" set excluding patients with major protocol violations and deviations. Only the analyses relating to the principal measure of efficacy were performed using this set. Any difference between this analysis and the analysis of the "full analysis" set was to be explored and explanations identified. All relevant protocol deviations were assessed under blind conditions and documented.

All patients taking at least one dose of study medication were included in the analysis of safety. No assessments were excluded from this set. The safety set was analysed as treated.

The treatment groups were assessed for comparability with respect to baseline information, in particular the BPI "worst pain" in the past 24 hours, ECOG performance status and nature of predominant pain. Any clinically significant difference was incorporated as a covariate into an additional sensitivity analysis.

For all efficacy variables 95% two-sided confidence intervals for the difference between hydromorphone and morphine were calculated.

The principal measure of efficacy was the mean of the last two post-baseline recorded values (or last value, if only one value is available) for "worst pain" in the past 24 hours. The two treatments were to be considered equivalent (for each phase separately) if the 95% two sided confidence interval for the difference between the adjusted means for the two treatments (taken from an analysis of covariance [Armitage 1987, p 282-95] with factors for treatment and country with the baseline value for "worst pain" used as a covariate) lay within -1.5 to 1.5. An additional analysis, including a factor for the treatment-by-country interaction was performed. If the interaction was significant at the 10% level, the source of the interaction and its impact on treatment equivalence was to be assessed. A sensitivity analysis was to be performed on CR phase data, if there was evidence of relevant treatment group differences in the IR phase. This analysis was to include additional covariates such as time in IR phase (in days) and "worst pain" at the end of the IR phase.

The 95% two-sided confidence interval for the treatment difference between the adjusted means for the following variables at endpoint in the IR and CR phases respectively were also calculated.

- least pain in the past 24 hours
- average pain
- pain relief
- each of the seven questions relating to how pain has interfered with their life
- sum of the seven questions relating to how pain has interfered with their life

The adjusted means were estimated using the same approach as for the principal measure with the score at baseline for the variable used as a covariate (no additional analyses, including a factor for the treatment-by-country interaction, were performed), although no actual equivalence region was defined.

The 95% two-sided confidence interval for the treatment difference between the adjusted means at endpoint in the IR and CR phases for the mean of the last two post-baseline days' values (or last value, if only one value is available) for "pain now" a.m. and p.m. was estimated using an analysis of variance with factors for treatment group and country. Data were not available at baseline for some patients for these two variables. Ninety-five percent confidence intervals were also calculated for the within treatment changes between the endpoint values for the IR and the CR phase for all the above variables.

The time (in days) to dose stabilisation during both phases was analysed by the logrank test (Armitage 1987, p 429-31). For the IR phase this was defined as the number of days in the phase. Patients who withdrew from the study or who were excluded from the IR per-protocol analysis because they were considered not to be dose stable were censored at the time of last IR phase dose. For the CR phase this was defined as the first occurrence where the patient was dose stable (i.e. on the same dose level) for at least two days and had adequate pain control (i.e. had taken no greater than three doses of breakthrough medication in the last 24 hours). Since pharmacokinetic steady state was not achieved with CR medication until 48 hours after the first dose or any dose level change, the data from the first two days of the CR phase was not used to calculate time to dose stabilisation. Thus, the earliest a patient could be declared dose stable during the CR phase was on CR day 4. Patients who did not become dose stabilised were to have their value censored at the time of their last CR phase dose.

Summary statistics with appropriate 95% two sided confidence intervals are presented for the following variables:

- the number of patients having to change CR dose level (patients with starting CR dose levels different to last IR dose levels were omitted from this analysis)
- the mean number of dose levels changed during the CR phase (patients with starting CR dose levels different to last IR dose levels were omitted from this analysis)
- number of breakthrough-pain medication doses taken on the last two post-baseline days of each phase

Extent of exposure was described by the number of days of treatment within each phase of the study, and the number of days on each dose level within each study phase. When two different dose levels were taken on the same day, only the higher dose level was counted for calculation purposes.

The general handling of adverse event data was the same as that described for the acute pain studies. For tabulations concerning the CR phase, events that started during the IR phase and continued into the CR phase were included. For the overall and CR phase adverse events tabulations, post-treatment emergent events were defined as those events that commenced more than two days after the last study non-breakthrough medication dose. For

the IR phase tabulations, post-treatment emergent events were defined as those events that commenced more than two days after the last study IR medication dose (for those patients who did not enter the CR phase) and any day after the last study IR medication dose (for those patients who did enter the CR phase). All adverse events with the onset date on the same day as the first IR dose were assumed treatment emergent.

The difference between the treatment groups in the proportion of patients with adverse events within each phase are presented together with 95% confidence intervals for the difference in the proportion. Also the differences between the treatment groups in the proportion of patients reporting the more frequently (i.e. reported by at least 5% of the study population) reported adverse events are presented.

For the commonly reported adverse events associated with morphine (Moulin 1996), an additional tabulation was produced of all events ongoing or starting during the double-blind phase. The ongoing adverse events were not included in the other adverse event tabulations mentioned above, as they were not regarded as treatment emergent.

Differences between the treatment groups in the proportion of patients withdrawing are presented together with 95% confidence intervals for the difference in the proportion. The time to withdrawal from the study (irrespective of phase) was analysed by the logrank test.

Statistical assumption checking, for parameters such as normality of distribution, was performed in the same way as described for the acute pain studies.

Assuming the variability (sd) to be 2.0 (estimated from a previous published data, Serlin 1995) and 90% power, then a sample size of 47 evaluable patients per group entering the CR phase was originally required. Assuming a 30% drop-out/non-evaluable patient rate in each treatment group, approximately 70 patients per group were required to be randomised. After complete data had been received for 55 randomised patients the variability for the principal measure of efficacy was estimated for both phases of the study. The new estimates were 2.24 for the IR phase and 2.50 for the CR phase. These two variability estimates were calculated by taking the root mean square error from analysis of covariance models with factors for treatment group and country with baseline "worst pain" score as a covariate for each phase separately. These two root mean square errors were the sole output from a

program that accessed the treatment code. An appointed independent person within the Biostatistics and Data Management department, who had access to the randomisation, ran this program. A member of the Company's Quality Assurance department witnessed the running of this program. Using the revised variability for the CR phase of 2.5 and assuming 90% power and a two-sided two-sample t-test, then 74 patients per group were required to enter the CR phase. As the IR phase dropout rate at the time of the calculation was 10%, 82 patients per group were required to be randomised into the study.

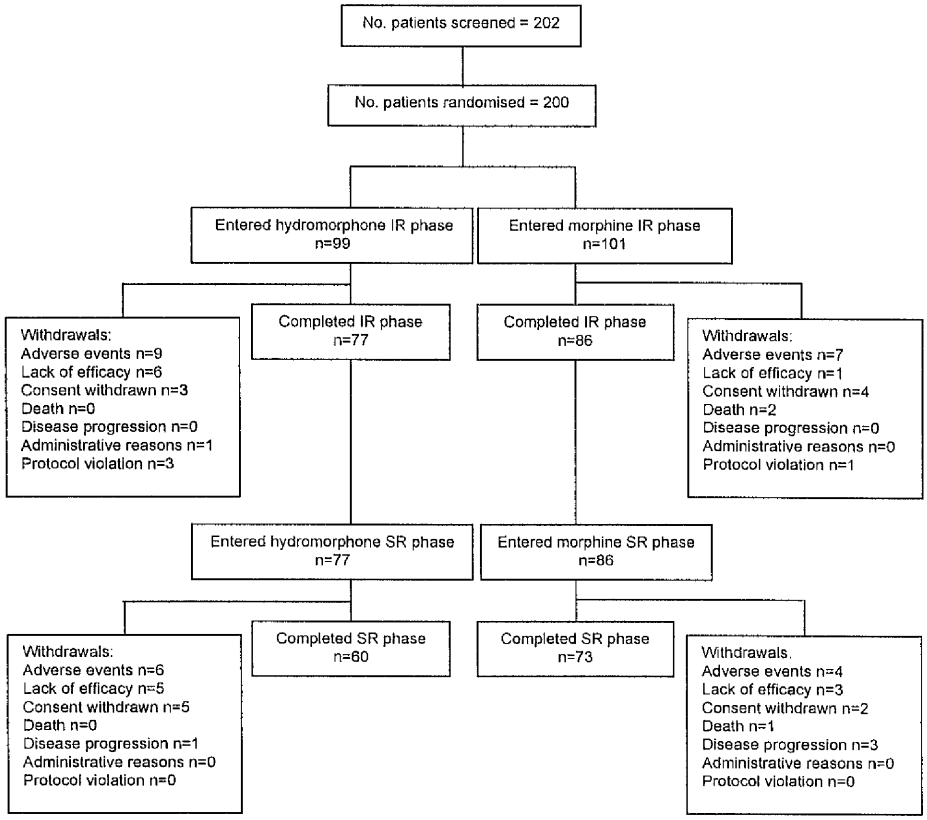
After data had been received for 120 randomised patients, the blinded variability for the principal measure of efficacy was estimated for the CR phase of the study. This estimate was 2.7. This variability was estimated by taking the root mean square error from an analysis of covariance model with a factor for country and a covariate for baseline "worst pain" score (i.e. no factor for treatment code was included). Using this revised variability and assuming 90% power and a two-sided two-sample t-test, then 84 patients per group were required to enter the CR phase. As the IR phase dropout rate was 18% at the time of the calculation, 100 patients per group were required to be randomised into the study.

The actual variability estimated from the root mean square error (MSE) from the analysis of covariance for the CR phase analysis was 2.46 for the "full analysis" set. The corresponding figure for the per-protocol set was 2.25.

5.4.5 Results

A total of 202 patients were screened for entry into the study between 28 June 1999 and 23 April 2001 of which 200 actually took study medication. Of the 200 patients randomised, 163 (82%) completed the IR phase and entered the CR phase and of these, 133 completed the CR phase (82%). Overall, 133/200 (67%) patients completed both phases of the study. A flow diagram of patient entry and completion is given below:

Figure 21. Flow diagram of patient entry and completion



Patients were recruited into the study from eight countries. Table 73 gives the number of patients completing and entering each of the double-blind phases of the study within each country:

Table 73. Summary of number of patients completing and entering each of the two double-blind phases of the study within each country

Country/ number of centres	IR phase			CR phase		
	Hydro-morphone	Morphine	Overall	Hydro-morphone	Morphine	Overall
United Kingdom						
8	21/34 (62%)	18/25 (72%)	39/59 (66%)	16/21 (76%)	16/18 (89%)	32/39 (82%)
Spain						
5	16/19 (84%)	19/21 (90%)	35/40 (88%)	12/16 (75%)	16/19 (84%)	28/35 (80%)
France						
4	3/3 (100%)	3/4 (75%)	6/7 (86%)	3/3 (100%)	2/3 (67%)	5/6 (83%)
Netherlands						
6	10/12 (83%)	16/17 (94%)	26/29 (90%)	9/10 (90%)	14/16 (88%)	23/26 (88%)
Germany						
4	3/6 (50%)	8/9 (89%)	11/15 (73%)	2/3 (67%)	7/8 (88%)	8/11 (80%)
Sweden						
3	5/5 (100%)	4/6 (67%)	9/11 (82%)	4/5 (80%)	4/4 (100%)	8/9 (89%)
Belgium						
5	14/15 (93%)	13/14 (93%)	27/29 (93%)	9/14 (64%)	9/13 (69%)	18/27 (67%)
Canada						
2	5/5 (100%)	5/5 (100%)	10/10(100%)	5/5 (100%)	5/5 (100%)	10/10(100%)
Total 37						
Overall	**77/99(78%)**	**86/101(85%)**	**163/200(82%)**	**60/77(78%)**	**73/86(85%)**	**133/163(82%)**

Withdrawals and reason for withdrawal, as recorded by the investigator, are summarised in Table 74. Although more patients withdrew from the hydromorphone group in each phase, the 95% confidence intervals for the difference in the proportion of patients withdrawing contained zero for each phase as was the case for both phases combined, implying these differences were not statistically significant. There was no statistically significant difference between treatment groups in the time to withdraw irrespective of phase (p=0.17). The Kaplan-Meier mean estimates were 16.5 days and 17.8 days for the hydromorphone and morphine groups respectively.

Table 74. Summary of patient withdrawals during the double-blind phase

Reason for withdrawal	IR phase		CR phase		Both phases	
	Hydro-morphone	Morphine	Hydro-morphone	Morphine	Hydro-morphone	Morphine
n	99	101	77	86	99	101
Adverse events	9 (9%)	7 (7%)	6 (8%)	4 (5%)	15 (15%)	11 (11%)
Lack of efficacy	6 (6%)	1 (1%)	5 (6%)	3 (3%)	11 (11%)	4 (4%)
Consent withdrawn	3 (3%)	4 (4%)	5 (6%)	2 (2%)	8 (8%)	6 (6%)
Death	-	2 (2%)	-	1 (1%)	-	3 (3%)
Disease progression	-	-	1 (1%)	3 (3%)	1 (1%)	3 (3%)
Administrative reasons	1 (1%)	-	-	-	1 (1%)	-
Protocol violation	3 (3%)	1 (1%)	-	-	3 (3%)	1 (1%)
Total withdrawn	22 (22%)	15 (15%)	17 (22%)	13 (15%)	39 (39%)	28 (28%)
Difference in the proportion of patients withdrawn	7%		7%		12%	
95% CI	-6%,21%		-8%,22%		-4%,28%	

Table 75 summarises major and minor protocol deviations during the study. Major protocol deviations led to exclusion of the patient from the per-protocol analysis of the relevant phase of the study.

Table 75. Summary of protocol deviations during the double-blind phase

Deviation[a]	Treatment group		Overall
	Hydromorphone	Morphine	
Major deviations			
Took strong opioids during study	1	2	3
Not dose stable at end of the IR phase	2	4	6
Not dose stable at end of the CR phase	4	4	8
Number of patients with major deviations	6	9	15
Minor deviations[b]			
Took weak opioids during study	7	4	11
Took adjuvant pain therapies (other than opioids) that did not remain at constant dosage during the study and which were taken for "pain-related" reasons	18	12	30
IR phase > 9 days	4	-	4
Started taking IR medication after entering CR phase	2	-	2
CR phase < 10 days and completed study	-	1	1
CR phase > 15 days	3	1	4
Starting CR dose level different to last IR dose level	3	4	7
Baseline laboratory assessments after first IR dose	5	2	7
Number of patients with minor deviations	35	21	56
Number of patients with a deviation	37	26	63

a Not mutually exclusive

b Includes two patients, one in each treatment group who were taking weak opioids for indications other than pain

5.4.5.1 Efficacy

A total of 200 patients entered the double-blind phase of the study; the number of patients providing data for the primary measure of efficacy within each phase of the study is given in Table 76. Two patients (numbers 287 and 322) provided no post-baseline efficacy data and therefore 198 patients were included in the "full analysis" set. A total of 193 (97%) patients provided at least one post-baseline "worst pain" score, although two of these patients did not provide post-baseline scores within the IR phase of the study.

Table 76. Summary of number of patients providing data for "worst pain" (primary measure of efficacy) within each phase of the study ("full analysis" set)

	IR phase			CR phase		
	Hyd.	Morphine	Overall	Hyd.	Morphine	Overall
Number entering phase	99	101	200	77	86	163
No post baseline data/no CR data	4	3	7	1	1	2
No baseline and IR follow-up data but completed the study	1	1	2	-	-	-
Completed study without CR data	-	-	-	-	1	1
Number providing data	94	97	191	76	84	160
No baseline	-	1	1	1	2	3
Number included in ANCOVA of "worst pain" at the end of each phase[a]	94	96	190	75	82	157

a Analysis required a "worst pain" score at baseline

The per-protocol analysis set included all patients in the "full analysis" set excluding the following:

- patients failing to complete the respective phase
- patients completing the respective phase but having less than two days of dose stable pain control at the end of the phase (For the IR phase, this was solely determined by the investigator's adjudication at the end of the phase. For the CR phase, a patient was considered not dose stable for analysis purposes, either if the patient was considered not dose stable by the question on the last available daily contact report, or if a dose of CR medication had been missed in the last 24 hours of the phase as recorded on the contact report)

The assessments subsequent to any use of other strong (i.e. not including agents such as codeine, tramadol) opioid analgesics were also excluded from the per-protocol analysis.

All efficacy variables were analysed using the "full analysis" set whereas the per-protocol set was restricted to the principal measure of efficacy. The number of patients providing data for the per-protocol analysis of this variable is given in Table 77.

Table 77. Summary of number of patients providing data for "worst pain" (primary measure of efficacy) within each phase of the study (per-protocol set)

	IR phase			CR phase		
	Hyd.	Morphine	Overall	Hyd.	Morphine	Overall
Number entering phase	99	101	200	77	86	163
Number providing data	94	97	191	76	84	160
Excluded from PP set						
Provided data but withdrew from phase	18	12	30	16	12	28
Took strong opioids but completed phase	1	1	2	-	1	1
Not dose stable but completed phase	2	4	6	4	4	8
Number excluded	21	17	38	20	17	37
Number included in PP* analysis	73	80	153	56	67	123
No baseline	-	1	1	1	2	3
Number included in ANCOVA of "worst pain" at the end of each phase[a]	73	79	152	55	65	120

* PP = "per protocol"

a Analysis required a "worst pain" score at baseline

The treatment groups were balanced in terms of age, sex, race and weight. Mean age was 59.8 years with range 19 to 82 years. One hundred and two patients (51%) were female. One hundred and ninety-seven (98.5%) patients were Caucasian, 2 (1%) Oriental and 1 (0.5%) patient was classified as "Other". Mean weight was 66.9 kg with range 35.0 to 110.0 kg.

Table 78. Entry profile: demographic information for all patients who took study treatment

Variable		Treatment group		Overall
		Hydromorphone	Morphine	
Total number of patients		99	101	200
Age (yr)	Mean	60.7	59.0	59.8
	sd	12.5	11.4	11.9
	n	99	101	200
	Range	27.0, 82.0	19.0, 81.0	19.0, 82.0
Sex	Female	53 (54%)	49 (49%)	102 (51%)
	Male	46 (46%)	52 (51%)	98 (49%)
Race	Caucasian	99	98	197
	Oriental	0	2	2
	Other	0	1	1
Weight (kg)	Mean	66.3	67.4	66.9
	sd	15.3	13.3	14.3
	n	96	99	195
	Range	35.0, 110.0	37.5, 96.0	35.0, 110.0

The most common cancer type was breast cancer recorded for 56 (28%) patients. Forty (20%) patients were recorded as having lung cancer and 38 (19%) gastrointestinal cancer. The most common location of metastases was bone which was recorded for 107 (54%) patients. A total of 133 (67%) patients had their predominant pain in bone or soft tissue, 34 (17%) had mixed pain, 33 (17%) had visceral pain and there were no reports of neuropathic pain. The lack of any patients with predominantly neuropathic pain probably reflects the investigators' belief that opioids are not of reliable benefit in this pain type (Arner 1988). Three (1.5%) patients had an ECOG score of 4 at baseline (worst category) with a further 32 (16%) having a score of 3. The mean ECOG score was 1.6. For the 195 patients with baseline data, the mean "worst pain" score was 6.3, a total of 21 (11%) patients had the maximum score of 10 and four (2%) patients reported no pain at baseline (Table 79). Thus, patients' self-reported pain from both extremes of the pain scale is present at the start of the study. This is entirely expected since on one hand, patients with satisfactory pain control could be enrolled into this study, and on the other hand, it could be expected that some investigators would use the study as an exercise in the management of the pain in a patient who was currently experiencing poor pain control. The latter scenario would most obviously be the case where patients were progressing to the use of strong opioids for the first time in their chronic pain management. Only 41% of patients were receiving strong opioids at baseline (Table 80).

Table 79. Cancer diagnosis, nature of predominant pain and baseline scores for ECOG and "worst pain" in the past 24 hours for all patients who took study treatment

		Treatment group		Overall
		Hydromorphone	Morphine	
Total number of patients		99	101	200
Cancer type	Breast	23	33	56
	Lung	20	20	40
	Bone	1	1	2
	Oral cavity	3	3	6
	Gastrointestinal	20	18	38
	Genitourinary	19	12	31
	Lymphoma	3	-	3
	Leukaemia	1	2	3
	Other	9	12	21
Location of metastases	None	11	15	26
	Brain	2	5	7
	Bone	48	59	107
	Bone marrow	3	2	5
	Lung	23	17	40
	Liver	19	21	40
	Kidney	1	1	2
	Lymph node	29	20	49
	Other	27	19	46
Nature of predominant pain	Visceral	19	14	33
	Bone or soft tissue	61	72	133
	Mixed	19	15	34
	Neuropathic	-	-	-
ECOG score at baseline[b]	0	1	5	6
	1	54	49	103
	2	28	28	56
	3	15	17	32
	4	1	2	3
	Mean	1.6	1.6	1.6
	sd	0.8	0.9	0.8
"worst pain" in the past 24 hours at baseline[c]	n (with data)	97	98	195
	Mean	6.3	6.2	6.3
	sd	2.7	2.5	2.6

a Not mutually exclusive
b 0 = patient fully active, able to carry out all-disease functions without restrictions, 1 = patient restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, 2 = patient ambulatory and capable of self care, but unable to work or carry out any work activities, up and about more than 50% of waking hours, 3 = patient capable of only limited self care, confined to bed or chair more than 50% of the waking hours, 4 = patient completely disabled, unable to carry on any self care, totally confined to bed or chair
c Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)

Table 80 summarises the various previous pain therapies reported. The two most common were morphine (68 patients) and tramadol (15 patients). A total of 81 (41%) patients reported the previous use of strong opioids.

Table 80. Summary of previous pain therapies

Therapy[a]	Treatment group		Overall
	Hydro-morphone (n=99)	Morphine (n=101)	(n=200)
Number of patients reporting a previous adjuvant pain therapy	50 (51%)	54 (54%)	104 (52%)
Strong opioids			
Number of patients reporting	39 (39%)	42 (42%)	81 (41%)
DIAMORPHINE	2	1	3
FENTANYL	2	2	4
KETOBEMIDONE	1	1	2
METHADONE	-	2	2
MORPHINE	32	36	68
PARACETAMOL + OXYCODONE	1	-	1
PETHIDINE	2	-	2
Weak opioids			
Number of patients reporting	17 (17%)	15 (15%)	32 (32%)
CODEINE	2	1	3
DIHYDROCODEINE	2	1	3
PARACETAMOL + CODEINE	2	3	5
PARACETAMOL + ASPIRIN + CAFFEINE + CODEINE	1	-	1
PARACETAMOL + CAFFEINE + CODEINE	1	-	1
PARACETAMOL + DEXTROPROPOXYPHENE	4	1	5
PARACETAMOL + DIHYDROCODEINE	-	2	2
TRAMADOL	7	8	15
Others			
Number of patients reporting	7 (7%)	9 (9%)	16 (16%)
ACETYLSALICYLIC ACID	-	1	1
BENZYDAMINE HYDROCHLORIDE	-	1	1
CLODRONATE DISODIUM	1	-	1
DEXAMETHASONE	1	-	1
DICLOFENAC	1	2	3
GABAPENTIN	1	-	1
HYDROCORTISONE	1	-	1
KETOROLAC	-	1	1
NALOXONE	1	1	2
NAPROXEN	1	2	3
PARACETAMOL	2	1	3
PREDNISOLONE	-	1	1

a Not mutually exclusive

Pain therapies ongoing or started during the study are summarised in Table 81. Three (2%) patients took strong opioids during the study (this was designated a major protocol violation) and 9 (5%) took weak opioids (a minor protocol violation). Thirty (15%) patients took adjuvant pain therapies (other than opioids) that did not remain at constant dosage during the study and which were taken for "pain-related" reasons. The patients who took strong opioids were excluded from the per-protocol analysis.

Table 81. Summary of pain therapies ongoing or starting during the double-blind phase

	Hydromorphone (n=99)	Morphine (n=101)	Overall (n=200)
Number of patients reporting a therapy[a]	63 (64%)	65 (64%)	128 (64%)
Strong opioid			
Number of patients reporting	1 (1%)	2 (2%)	3 (2%)
MORPHINE	1	2	3
Weak opioid			
Number of patients reporting	6 (6%)	3 (3%)	9 (5%)
CODEINE PHOSPHATE	1	-	1
DIHYDROCODEINE	2	-	2
PARACETAMOL+CODEINE	1	1	2
PARACETAMOL+DEXTROPROPOXYPHENE	-	1	1
TRAMADOL	2	1	3
Steroid			
Number of patients reporting	12 (12%)	18 (18%)	30 (15%)
BETAMETHASONE	-	2	2
DEXAMETHASONE	8	13	21
PREDNISOLONE	1	-	1
PREDNISOLONE SODIUM SULFOBENZOATE	-	1	1
PREDNISONE	4	2	6
NSAID			
Number of patients reporting	29 (29%)	35 (35%)	64 (32%)
DICLOFENAC	17	15	32
DICLOFENAC+MISOPROSTOL	1	-	1
DIFLUNISAL	2	-	2
FLURBIPROFEN	1	4	5
IBUPROFEN	3	4	7
INDOMETACIN	3	5	8
NAPROXEN	5	6	11
NSAID'S	-	1	1
ROFECOXIB	-	1	1
Simple analgesic			
Number of patients reporting	26 (26%)	20 (20%)	46 (23%)
ACETYLSALICYLATE LYSINE	-	1	1
ACETYLSALICYLIC ACID	1	-	1
FLUPIRTINE	1	-	1
METAMIZOLE	6	3	9
METHYLPREDNISOLONE	1	-	1
PARACETAMOL	19	16	35
Antidepressant			
Number of patients reporting	13 (13%)	13 (13%)	26 (13%)
AMITRIPTYLINE	7	8	15
DOSULEPIN	5	4	9
IMIPRAMINE	1	-	1
NORTRIPTYLINE	-	1	1
Anticonvulsant			
Number of patients reporting	9 (9%)	8 (8%)	17 (9%)
CARBAMAZEPINE	1	2	3
GABAPENTIN	5	5	10
VALPROATE SODIUM	3	1	4
Miscellaneous adjuvant			
Number of patients reporting	3 (3%)	6 (6%)	9 (5%)
CLODRONATE DISODIUM	1	4	5
CLONIDINE	1	-	1
PAMIDRONATE DISODIUM	1	2	3

[a] not mutually exclusive

The mean of the last two recorded scores for "worst pain" at the end of each of the respective study phases were the principal measure of efficacy for the "full analysis" set. These are presented in Table 82. For the two treatments to be considered equivalent the

95% two-sided confidence interval for the difference between the adjusted means for the two treatments had to lie within -1.5 to 1.5. This was the case for the IR phase, indicating that hydromorphone IR was equivalent to morphine IR. For the CR phase, the lower limit was less than –1.5 which implied the superiority of hydromorphone could not be disproved. However, the upper limit was less than 1.5 and therefore non-inferiority of hydromorphone was proven. Furthermore there was a statistically significant difference between the treatment groups in favour of hydromorphone for the CR phase. The adjusted mean for hydromorphone was 3.5 compared to 4.3 for morphine (p=0.046). For both phases, the term for baseline score was highly statistically significant (p<0.001). The term for treatment group-by-country interaction was statistically significant at the 10% level for the IR phase analysis (p=0.08). "Worst pain" decreased during the study in both treatment groups. For the cohort of patients with data for both phases, mean "worst pain" decreased by 1.0 (95% CI 0.5,1.6) for hydromorphone-treated patients from the end of the IR phase to the end of the CR phase. For the morphine-treated patients, mean "worst pain" decreased by 0.5 (95% CI –0.1,1.0). Figure 22 presents the mean "worst pain" profiles during the whole of the study for the observed datasets based on the "full analysis" set.

Table 82. Analysis of covariance for the mean of the last two recorded scores for "worst pain" ("full analysis" set)

Mean of the last two recorded scores for "worst pain"[a]	IR phase			CR phase		
	Hydromorphone		Morphine	Hydromorphone		Morphine
Total number of patients	94		97[b]	76[b]		84[c]
Mean	5.0		4.8	3.5		4.1
sd	2.7		2.4	2.5		2.7
Range	0,10		0,9	0,10		0,9.5
Adjusted mean[d]	5.0		4.8	3.5		4.3
Difference in adjusted means[e]		0.2			-0.8	
se (of difference)		0.3			0.4	
95% CI for difference		-0.4,0.9			-1.6,-0.01	
	n		Mean	se		95% CI
CR – IR (Hydromorphone)	75		-1.0	0.3		-1.6,-0.5
CR – IR (Morphine)	83		-0.5	0.3		-1.0,0.1
Analysis of covariance	F	df	p	F	df	p
Baseline score	58.35	1,180	<0.001	21.52	1,147	<0.001
Treatment group	0.41	1,180	0.52	4.04	1,147	0.046
Country	0.31	7,180	0.95	0.45	7,147	0.87
Treatment group-by-country	1.83	7,173	0.08	1.72	7,140	0.11

a Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)
b One patient did not provide a baseline score so not included in ANCOVA
c Two patients did not provide a baseline score so not included in ANCOVA
d Adjusted for baseline and country
e A negative difference favours hydromorphone

Figure 22. Mean profile with standard error bars for worst pain during the whole of the study (observed data – "full analysis" set)

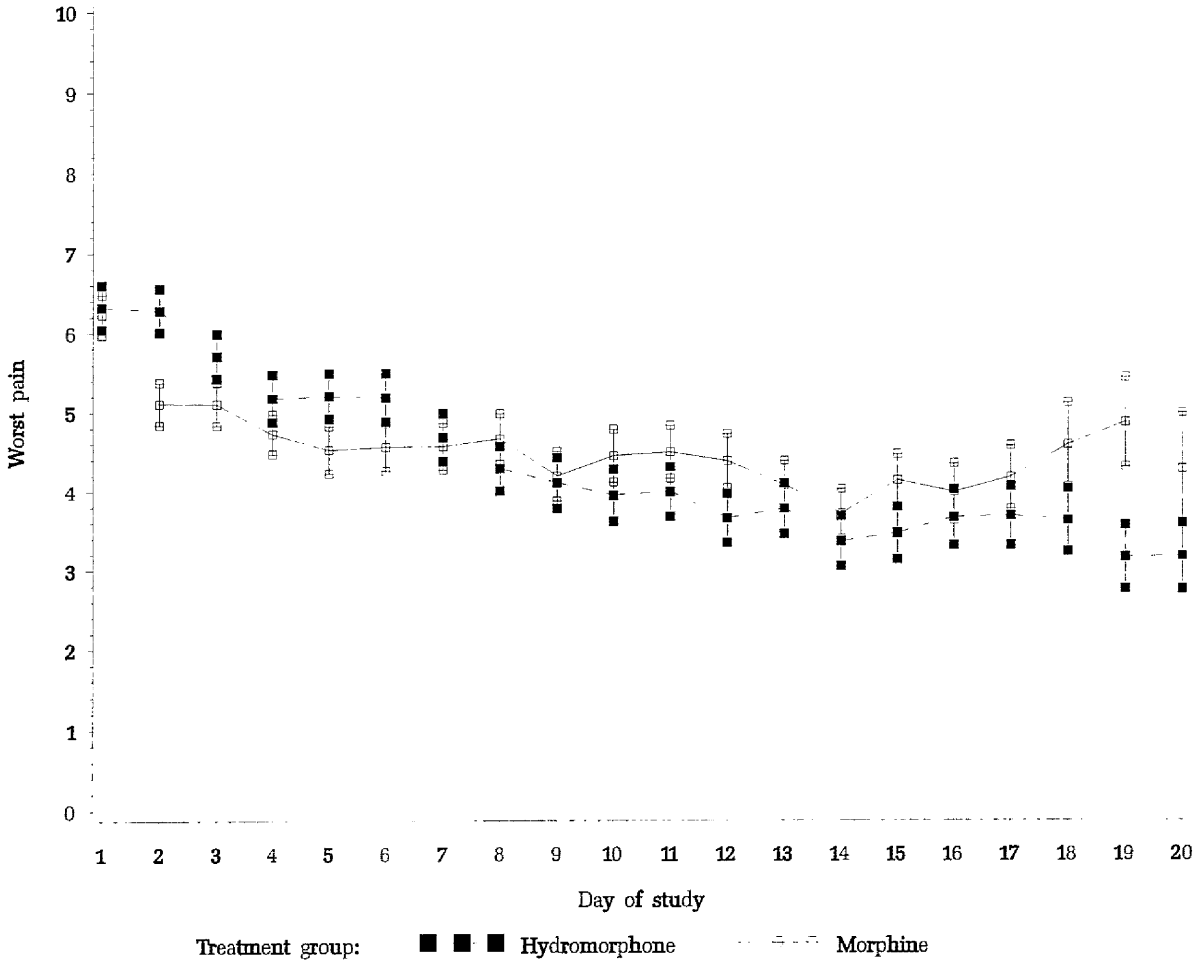


Table 83 presents the results from the per-protocol analysis of the above. The conclusions were the same, with statistical significance in favour of hydromorphone at the end of the CR phase (p=0.049). The adjusted means were 2.9 for hydromorphone and 3.8 for morphine. The lower limit of the 95% CI was again less than -1.5 implying the superiority of hydromorphone could not be disproved. The treatment group-by-country interaction was statistically significant at the 10% level in both phases (p=0.04 for the IR phase and p=0.098 for the CR phase).

Table 83. Analysis of covariance for the mean of the last two recorded scores for "worst pain" ("per protocol" set)

Mean of the last two recorded scores for "worst pain"[a]	IR phase			CR phase		
	Hydromorphone		Morphine	Hydromorphone		Morphine
Total number of patients	73		80[b]	56[b]		67[c]
Mean	4.5		4.5	3.0		3.7
sd	2.6		2.4	2.1		2.5
Range	0,10		0,9	0,8		0,9.5
Adjusted mean[d]	4.6		4.8	2.9		3.8
Difference in adjusted means[e]		-0.2			-0.8	
se (of difference)		0.3			0.4	
95% CI for difference		-0.9,0.5			-1.7,-0.004	
	n		Mean	se		95% CI
CR – IR (Hydromorphone)	55		-1.4	0.3		-2.1,-0.7
CR – IR (Morphine)	63		-0.5	0.3		-1.1,0.1
Analysis of covariance	F	df	p	F	df	p
Baseline score	60.95	1,142	<0.001	15.89	1,110	<0.001
Treatment group	0.28	1,142	0.60	3.96	1,110	0.049
Country	0.40	7,142	0.90	0.80	7,110	0.59
Treatment group-by-country	2.21	7,135	0.04	1.79	7,103	0.098

a Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)
b One patient did not provide a baseline score so not included in ANCOVA
c Two patients did not provide a baseline score so not included in ANCOVA
d Adjusted for baseline and country
e A negative difference favours hydromorphone

Removal from the per-protocol analysis of the patients from three of the four poorest recruiting counties rendered the treatment group-by-centre term not statistically significant (omitting Canada p=0.23, omitting France p=0.20 and omitting Germany p=0.12), the only exception being Sweden where hydromorphone was favoured (p=0.03). Furthermore for the four largest recruiting countries the adjusted treatment means always strongly favoured hydromorphone. Table 84 presents the adjusted means for each treatment group by country for the per-protocol analysis of the CR phase data.

Table 84. Adjusted treatment means by country from the analysis of covariance for the mean of the last two recorded scores for "worst pain" at the end of the CR phase (per-protocol set)

Country	Adjusted means[a] for "worst pain"[b] at the end of the CR phase	
	Hydromorphone (n=55)	Morphine (n=65)
United Kingdom (n=29)	1.8 (n=14)	4.0 (n=15)
Spain (n=24)	3.4 (n=11)	3.6 (n=13)
Netherlands (n=20)	2.8 (n=8)	4.2 (n=12)
Belgium (n=17)	1.9 (n=9)	3.6 (n=8)
Canada (n=9)	5.4 (n=4)	3.5 (n=5)
Germany (n=9)	4.6 (n=2)	3.3 (n=7)
Sweden (n=8)	3.8 (n=4)	4.5 (n=4)
France (n=4)	3.1 (n=3)	0.0 (n=1)

a From analysis of covariance, adjusted for baseline, treatment group and country
b Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)

For the 157 patients who provided baseline and endpoint CR phase "worst pain" data in the "full analysis" set, there was an imbalance between the treatment groups in the total days of IR phase exposure. For these patients, mean exposure to hydromorphone was 6.0 days (n=75) compared to 4.8 days (n=82) exposure to morphine. As a result of this imbalance sensitivity analyses were performed on the CR phase data for the "full analysis" and per-protocol sets introducing two extra covariates in the analysis of covariance. These were the mean of the last two recorded scores for "worst pain" at the end of IR phase and length of IR phase (in days). The results of these analyses are presented in Table 85. In both cases, the treatment group comparisons were again statistically significantly in favour of hydromorphone ($p=0.03$ in both cases) and the lower limit of the 95% CI was again less than -1.5 implying the superiority of hydromorphone could not be disproved. In addition, the covariate for "worst pain" at the end of the IR phase was significant ($p<0.001$ in both cases) and the covariate for length of IR phase was not significant ($p=0.17$ and $p=0.47$ for the IR and CR phases respectively).

Table 85. Analysis of covariance for the mean of the last two recorded scores for "worst pain" in the CR phase with additional covariates for length of IR phase and "worst pain" at the end of the IR phase ("full analysis" and per-protocol sets)

Mean of the last two recorded scores for "worst pain" for the CR phase[a]	"Full analysis" set			Per-protocol set		
	Hydromorphone		Morphine	Hydromorphone		Morphine
Total number of patients	76[b]		84[c]	56[b]		67[c]
Mean	3.5		4.1	3.0		3.7
sd	2.5		2.7	2.1		2.5
Range	0,10		0,9.5	0,8		0,9.5
Adjusted mean[d]	3.4		4.3	2.9		3.8
Difference in adjusted means[e]		-0.8			-0.9	
se (of difference)		0.4			0.4	
95% CI for difference		-1.6,-0.06			-1.7,-0.1	
Anaiysis of covariance	F	df	p	F	df	p
Baseline score	0.68	1,145	0.41	0.86	1,108	0.36
"Worst pain" at end of IR phase	27.23	1,145	<0.001	14.58	1,108	<0.001
Length of IR phase (in days)	1.91	1,145	0.17	0.54	1,108	0.47
Treatment group	4.54	1,145	0.03	4.74	1,108	0.03
Country	0.74	7,145	0.64	0.73	7,108	0.64

a Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)
b One patient did not provide a baseline score so not included in ANCOVA
c Two patients did not provide a baseiine score so not included in ANCOVA
d Adjusted for baseline and country
e A negative difference favours hydromorphone

Table 86 summarises the results from the analyses of the secondary efficacy variables derived from the BPI.

Table 86. Summary of analyses for each of the variables from the BPI questionnaire by study phase ("full analysis" set)

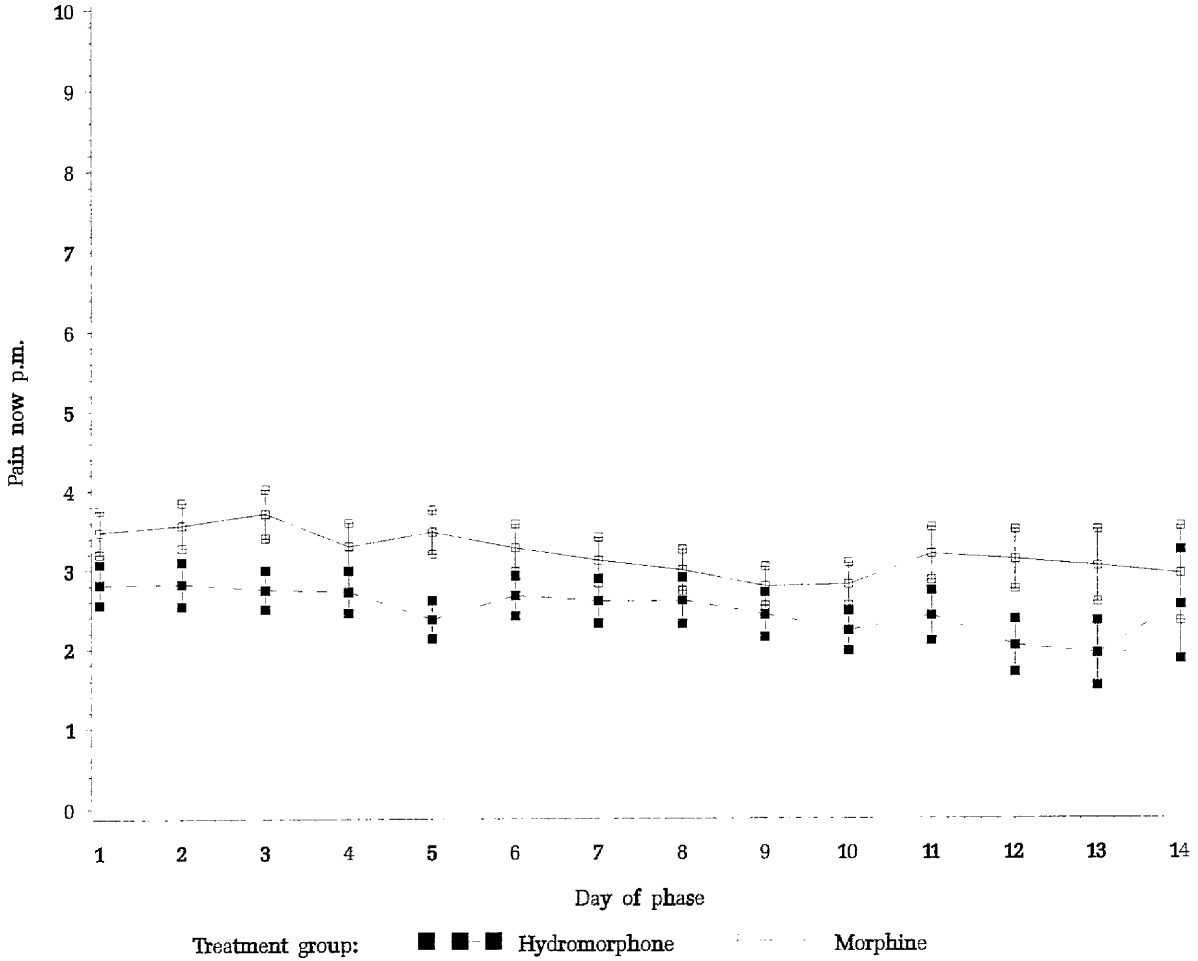
Variable	Adjusted means[a] for IR phase			Adjusted means[a] for CR phase		
	Hyd.	Morphine	Difference[b] (95% CI)	Hyd.	Morphine	Difference[b] (95% CI)
Least pain[c]	1.8	2.2	-0.4 (-0.9,0.1)	1.8	1.8	0.1 (-0.5,0.6)
Average pain[c]	3.6	3.6	0.1 (-0.5,0.6)	3.3	3.3	0.05 (-0.6,0.7)
Pain now am[c]	3.3	3.3	0.01 (-0.7,0.7)	2.5	2.8	-0.4 (-1.1,0.3)
Pain now pm[c]	3.6	3.6	0.02 (-0.7,0.7)	2.6	3.3	-0.6 (-1.4,0.1)
Pain relief[d]	64.2	65.6	-1.3 (-8.2,5.5)	69.8	69.3	0.4 (-7.4,8.3)
How pain had interfered with						
General activity[e]	4.2	4.2	-0.02 (-0.8,0.8)	3.7	4.1	-0.5 (-1.4,0.5)
Mood[e]	3.2	3.3	-0.1 (-0.8,0.6)	3.0	3.1	-0.1 (-1.0,0.7)
Walking ability[e]	3.6	3.8	-0.2 (-1.0,0.6)	3.8	3.8	-0.03 (-1.0,0.9)
Normal work[e]	4.6	5.4	-0.8 (-1.6,-0.01)[f]	4.6	4.8	-0.2 (-1.2,0.9)
Relations with other people[e]	2.5	2.3	0.2 (-0.6,0.9)	2.7	2.5	0.1 (-0.7,1.0)
Sleep[e]	2.4	2.1	0.2 (-0.4,0.9)	1.8	2.3	-0.5 (-1.3,0.3)
Enjoyment of life[e]	4.1	4.0	0.2 (-0.7,1.0)	3.6	3.5	0.1 (-0.9,1.0)
Sum of the seven variables	23.9	23.6	0.3 (-3.9,4.5)	23.0	23.4	-0.3 (-5.6,5.0)

a Adjusted for baseiine (if appropriate) and country from ANOVA/ANCOVA
b A negative difference favours hydromorphone
c Measured on a 11-point scale (0 = no pain; 10 = pain as bad as you can imagine)
d Measured on a 11-point scale (0% = no relief; 100% = complete relief)
e Measured on a 11-point scaie (0 = does not interfere; 10 = completely interferes)
f Treatment p-value = 0.046

The lack of differences in these measures confirmed the expectations that "worst pain" is the most sensitive measure in the BPI. The one significant (at the 5% level) difference (normal work) is probably only a consequence of multiple testing.

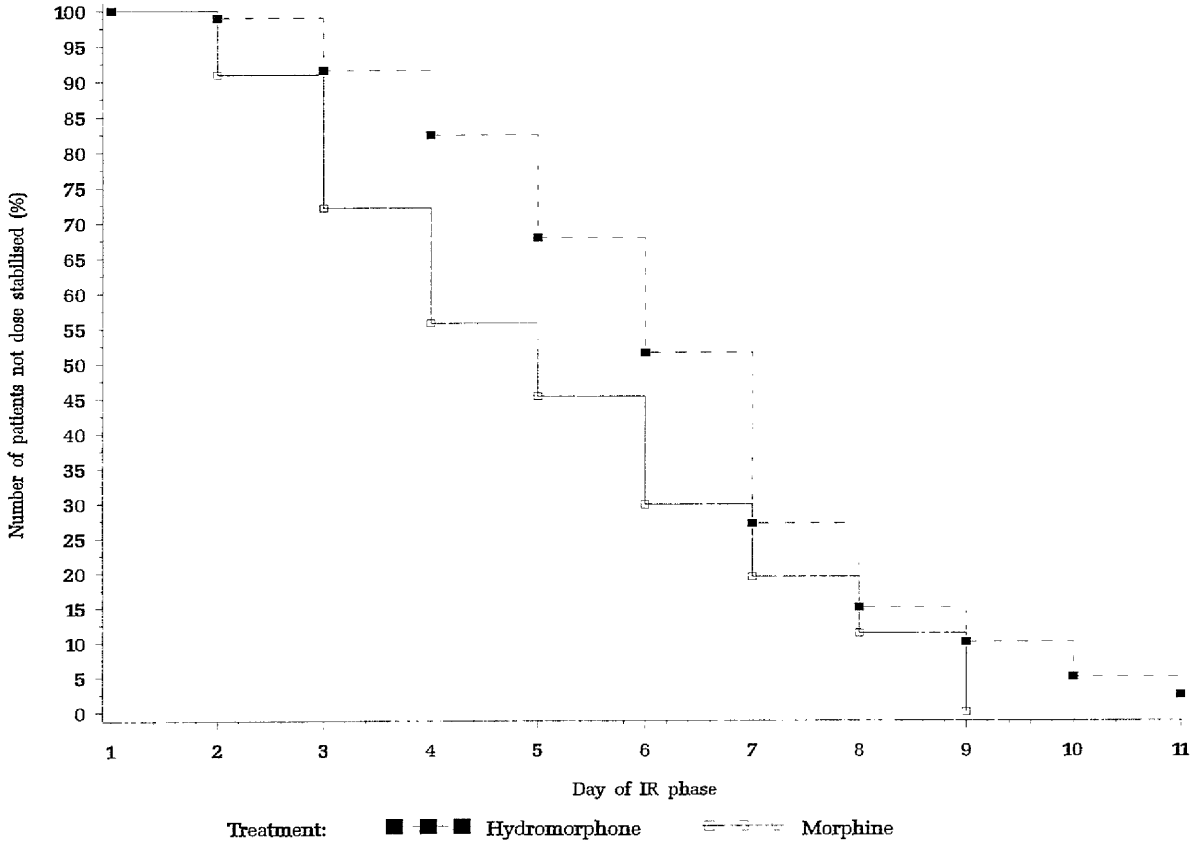
There was, however, a trend in favour of hydromorphone for the mean of two last recorded scores for "pain now" p.m. at the end of CR phase, although the treatment group difference was not statistically significant (p=0.09). Figure 23 presents the mean "pain now" p.m. profiles during the CR phase for the observed and carryforward datasets.

Figure 23. Mean profile with standard error bars for pain "now" p.m. during the CR phase (observed data - "full analysis" set)



Patients in the hydromorphone group took longer to dose stabilise in the IR phase. The mean Kaplan-Meier estimates for the time to stabilise in this phase were 6.5 and 5.2 days for the hydromorphone and morphine groups respectively (p=0.0013). The actual percentage of patients dose stabilised at the end of IR phase was 74% (hydromorphone) and 80% (morphine). There was no difference between the treatment groups in the time to dose stabilisation in the CR phase. The mean Kaplan-Meier estimates for the time to stabilise in this phase were 4.3 and 4.6 days for the hydromorphone and morphine groups, respectively (p=0.39). The actual percentage of patients dose stabilised at least once during the CR phase was 92% (hydromorphone) and 94% (morphine). Figure 24 presents the Kaplan-Meier estimates for time to dose stabilisation for the IR phase.

Figure 24. Kaplan-Meier estimates for time to dose stabilisation in the IR phase



Eighteen out of 74 (24%) patients in the hydromorphone treatment group had to change their dose level during the CR phase compared to 23/82 (28%) patients in the morphine treatment group. Of the 18 patients who had CR dose level changes in the hydromorphone group, 14 had one change and four had two changes. Of the 23 patients who had CR dose level changes in the morphine treatment group there were 16 and seven patients having one and two dose level changes, respectively. Seven patients (three in the hydromorphone treatment group and four in the morphine treatment group) with starting CR dose levels different to last IR dose were omitted from these analyses.

In the IR phase, a higher proportion of patients in the hydromorphone treatment group (65%) were using breakthrough pain medication on the last two days of the IR phase compared with the morphine treatment group (54%). The adjusted mean number of breakthrough pain medication doses were 2.1 for the hydromorphone treatment group and 1.4 for the morphine treatment group and the difference between the treatment groups was statistically significant (p=0.02). At the end of the CR phase, the number of patients using breakthrough pain medication was similar in the morphine group (53%) compared with the hydromorphone group (51%). The adjusted mean number of breakthrough pain medication doses taken on the last two days of the CR phase were 1.7 for the hydromorphone treatment group and 1.5 for the morphine treatment group; there was no statistically significant difference (p=0.52) between the two treatment groups.

5.4.5.1.1 Statistical/analytical issues

There were significant treatment group-by-country interactions for the analysis of the primary variable of "worst pain". This can be explained by the countries which recruited the largest number of patients favouring hydromorphone whilst countries which recruited smaller numbers of patients in general favoured morphine.

5.4.5.1.2 Efficacy conclusions

Hydromorphone IR was equivalent to morphine IR for the primary variable of "worst pain". For the CR treatments, the superiority of hydromorphone to morphine for the primary variable could not be disproved; however, non-inferiority of hydromorphone to morphine was proven and there was a statistically significant difference in favour of hydromorphone for the CR phase. The secondary efficacy measures did not have any signficant differences,

but there was a trend towards a superior outcome for the hydromorphone group in the SR phase for "pain now" in the evening.

5.4.5.2 Safety

Table 87 summarises the number of days of treatment within each phase of the study and for both phases combined, by treatment group. The mean exposure to hydromorphone in the IR phase (5.7 days) was higher than the equivalent figure for morphine (4.7 days). Mean exposure in the CR phase for the two treatment groups was very similar: 11.4 days for hydromorphone and 11.5 days for morphine.

Table 87. Extent of exposure by study phase and overall

Exposure (number of days)[a]	Treatment group	
	Hydromorphone	Morphine
IR phase		
n	99	101
Mean	5.7	4.7
sd	2.2	2.1
Median	6.0	4.0
Range	1,11	1,9
Total exposure	562	479
CR phase		
n	77	86
Mean	11.4	11.5
sd	3.2	3.3
Median	12.0	12.0
Range	1,17	1,16
Total exposure	878	986
Both phases combined		
n	99	101
Mean	14.4	14.4
sd	6.5	5.6
Median	17.0	16.0
Range	1,24	1,22
Total exposure	1426	1454

a Day of last dose – day of first dose +1

Table 88 summarises the extent of exposure as total mg per day.

Table 88. Extent of exposure (total mg/day consumption)

	Treatment group	
	Hydromorphone	Morphine
IR phase		
n	99	101
Mean	28.0	129.0
sd	20.0	86.8
Median	22.3	106.7
Range	12,96	60,540
CR phase		
N	77	86
Mean	35.4	151.8
Sd	23.4	95.6
Median	29.1	120.0
Range	16,96	60,520

Table 89 summarises the endpoint dose level for each study phase by treatment group. A total of 70/101 (69%) of morphine-treated patients were receiving either dose level 1 and 2 at the end of the IR phase compared to 55 (56%) of hydromorphone-treated patients. At the end of the CR phase, 8/77 (10%) of hydromorphone-treated patients were receiving dose level 6 compared to 2/86 (2%) of morphine-treated patients.

Table 89. Endpoint dose level for each study phase

Endpoint dose	IR phase		CR phase	
level	Hydromorphone	Morphine	Hydromorphone	Morphine
n	99	101	77	86
1	33 (33%)	40 (40%)	22 (29%)	25 (29%)
2	22 (22%)	30 (30%)	14 (18%)	23 (27%)
3	23 (23%)	11 (11%)	17 (22%)	15 (17%)
4	9 (9%)	14 (14%)	11 (14%)	13 (15%)
5	6 (6%)	5 (5%)	5 (6%)	8 (9%)
6	6 (6%)	1 (1%)	8 (10%)	2 (2%)
Mean	2.5	2.2	2.8	2.6

The number of patients reporting an event and the number of events reported within each phase and for both phases combined by treatment group are summarised in Table 90 below. A higher proportion of hydromorphone-treated patients reported adverse events in the IR phase than morphine-treated patients with the opposite being the case in the CR phase. There was, however, no statistically significant difference between the treatments for the number of patients reporting adverse events. Overall, irrespective of study phase, 80/99

(81%) hydromorphone-treated patients reported 347 adverse events compared to 90/101 (89%) patients in the morphine treatment group who reported 355 adverse events.

Table 90. Summary of treatment emergent adverse events reported during the double-blind phase

	Treatment group	
	Hydromorphone	Morphine
IR phase		
Total number of patients	99	101
Number of patients reporting an adverse event	66 (67%)	61 (60%)
Difference in proportion of patients reporting (95% CI)	6% (-10%,23%)	
Number of events reported	191	163
CR phase[a]		
Total number of patients	77	86
Number of patients reporting an adverse event	61 (79%)	75 (87%)
Difference in proportion of patients reporting (95% CI)	-8% (-22%,6%)	
Number of events reported	229	256
Both phases combined		
Total number of patients	99	101
Number of patients reporting an adverse event	80 (81%)	90 (89%)
Difference in proportion of patients reporting (95% CI)	-8% (-20%,4%)	
Number of events reported	347	355

a Events that started during the IR phase and continued into the CR phase are included in these figures

The severity and relationship to therapy of adverse events reported within each phase and for both phases combined by treatment group are summarised in Table 91. Overall the majority of adverse events were mild or moderate in severity. A total of 73/347 (21%) of adverse events during hydromorphone therapy had definite or probable relationship to therapy compared to 97/355 (27%) during morphine therapy.

Table 91. Summary of severity and relationship to therapy of treatment emergent adverse events during the double-blind phase

		No of reports	
		Treatment group	
		Hydromorphone	Morphine
IR phase			
Severity	Mild	88 (46%)	85 (52%)
	Moderate	82 (43%)	58 (36%)
	Severe	20 (10%)	19 (12%)
	Unknown	1 (1%)	1 (1%)
Relationship to therapy	Definite	8 (4%)	12 (7%)
	Probable	50 (26%)	41 (25%)
	Possible	50 (26%)	41 (25%)
	Unlikely	33 (17%)	23 (14%)
	None	50 (26%)	46 (28%)
CR phase[a]			
Severity	Mild	97 (42%)	116 (45%)
	Moderate	104 (45%)	98 (38%)
	Severe	28 (12%)	40 (16%)
	Unknown	-	2 (1%)
Relationship to therapy	Definite	6 (3%)	12 (5%)
	Probable	30 (13%)	51 (20%)
	Possible	57 (25%)	54 (21%)
	Unlikely	50 (22%)	56 (22%)
	None	86 (38%)	83 (32%)
Both phases combined			
Severity	Mild	152 (44%)	167 (47%)
	Moderate	152 (44%)	130 (37%)
	Severe	42 (12%)	55 (15%)
	Unknown	1 (0.3%)	3 (1%)
Relationship to therapy	Definite	10 (3%)	19 (5%)
	Probable	63 (18%)	78 (22%)
	Possible	91 (26%)	81 (23%)
	Unlikely	70 (20%)	67 (19%)
	None	113 (33%)	110 (31%)

a Events that started during the IR phase and continued into the CR phase are included in these figures

The most commonly reported events (i.e. reported by at least 5% of patients in any treatment group) are summarised in Table 92.

Table 92. Summary of treatment emergent adverse events reported by at least 5% of patients in any treatment group during double-blind phase

MedDRA preferred term	Number of patients reporting		
	Treatment group		
	Hydromorphone	Morphine	Difference in proportion reporting (95% CI)
IR phase	**N=99**	**N=101**	
CONSTIPATION	22 (22%)	10 (10%)	12% (0%,25%)
NAUSEA	18 (18%)	20 (20%)	-2% (-15%,12%)
VOMITING	16 (16%)	21 (21%)	-5% (-18%,9%)
SOMNOLENCE	10 (10%)	11 (11%)	-1% (-11%,10%)
DIZZINESS (EXC VERTIGO)	8 (8%)	6 (6%)	2% (-7%,11%)
HEADACHE	8 (8%)	6 (6%)	2% (-7%,11%)
DIARRHOEA	8 (8%)	1 (1%)	7% (0%,14%)
PRURITUS	5 (5%)	4 (4%)	1% (-6%,8%)
ASTHENIA	5 (5%)	3 (3%)	2% (-5%,9%)
ABDOMINAL PAIN	5 (5%)	1 (1%)	4% (-2%,10%)
CR phase[a]	**N=77**	**N=86**	
CONSTIPATION	28 (36%)	19 (22%)	14% (-3%,31%)
NAUSEA	15 (19%)	23 (27%)	-7% (-23%,9%)
SOMNOLENCE	8 (10%)	9 (10%)	-0% (-12%,11%)
ASTHENIA	8 (10%)	8 (9%)	1% (-10%,12%)
VOMITING	7 (9%)	19 (22%)	-13% (-26%,0%)
CONFUSION	7 (9%)	2 (2%)	7% (-2%,16%)
DIARRHOEA	6 (8%)	2 (2%)	5% (-3%,14%)
PYREXIA	6 (8%)	1 (1%)	7% (-1%,14%)
INSOMNIA	5 (6%)	4 (5%)	2% (-7%,11%)
ANXIETY	5 (6%)	-	6% (-0%,13%)
ANOREXIA	4 (5%)	5 (6%)	-1% (-9%,8%)
ABDOMINAL PAIN	4 (5%)	4 (5%)	1% (-8%,9%)
PRURITUS	4 (5%)	4 (5%)	1% (-8%,9%)
DIZZINESS (EXC VERTIGO)	3 (4%)	8 (9%)	-5% (-15%,4%)
ANAEMIA	2 (3%)	5 (6%)	-3% (-11%,4%)
CONDITION AGGRAVATED	1 (1%)	5 (6%)	-5% (-11%,2%)
OEDEMA LOWER LIMB	1 (1%)	5 (6%)	-5% (-11%,2%)
Both phases combined	**N=99**	**N=101**	
CONSTIPATION	32 (32%)	25 (25%)	8% (-8%,23%)
NAUSEA	28 (28%)	34 (34%)	-5% (-21%,10%)
VOMITING	18 (18%)	27 (27%)	-9% (-23%,6%)
SOMNOLENCE	13 (13%)	16 (16%)	-3% (-15%,9%)
DIARRHOEA	13 (13%)	3 (3%)	10% (1%,19%)
ASTHENIA	10 (10%)	9 (9%)	1% (-9%,11%)
HEADACHE	10 (10%)	6 (6%)	4% (-5%,13%)
DIZZINESS (EXC VERTIGO)	9 (9%)	12 (12%)	-3% (-13%,8%)
CONFUSION	8 (8%)	3 (3%)	5% (-3%,13%)
PRURITUS	7 (7%)	7 (7%)	0% (-9%,9%)
PYREXIA	7 (7%)	2 (2%)	5% (-2%,12%)
ABDOMINAL PAIN	6 (6%)	4 (4%)	2% (-5%,10%)
INSOMNIA	5 (5%)	5 (5%)	0% (-7%,7%)
ANXIETY	5 (5%)	-	5% (-0%,10%)
ANOREXIA	4 (4%)	7 (7%)	-3% (-11%,5%)
ANAEMIA	4 (4%)	6 (6%)	-2% (-9%,5%)
SWEATING INCREASED	3 (3%)	5 (5%)	-2% (-9%,5%)
OEDEMA LOWER LIMB	2 (2%)	6 (6%)	-4% (-11%,3%)
CONDITION AGGRAVATED	1 (1%)	6 (6%)	-5% (-11%,1%)
URINARY TRACT INFECTION	1 (1%)	5 (5%)	-4% (-10%,2%)
NAUSEA AGGRAVATED	-	5 (5%)	-5% (-10%,0%)

a Events that started during the IR phase and continued into the CR phase are included in these figures

Table 93 lists the number of patients who had the commonly reported side effects associated with morphine (Moulin 1996) ongoing or starting during the double-blind phase. This table includes patients who had ongoing adverse events at the time of randomisation which were not attributable to treatment and were therefore not included in other Tables of adverse events. The proportion of patients reporting these adverse events during hydromorphone treatment was similar to that reported for morphine treatment.

Table 93. Summary of adverse events commonly reported with morphine ongoing or starting during double-blind phase

Adverse event (associated MedDRA preferred terms)	Number of patients reporting	
	Treatment group	
	Hydromorphone (n=99)	Morphine (n=101)
ABDOMINAL PAIN (abdominal pain , abdominal pain upper)	6 (6%)	8 (8%)
BLURRED VISION (diplopia)	-	1 (1%)
CONFUSION (confusion, disorientation)	8 (8%)	5 (5%)
CONSTIPATION (constipation, constipation aggravated)	34 (34%)	25 (25%)
DIARRHOEA (diarrhoea)	13 (13%)	3 (3%)
DIZZINESS (dizziness (exc. vertigo))	9 (9%)	12 (12%)
DRY MOUTH (dry mouth)	4 (4%)	3 (3%)
FATIGUE (asthenia, fatigue, fatigue aggravated, lethargy, malaise, sedation, sedation aggravated, somnolence, weakness)	24 (24%)	29 (29%)
ITCHING (pruritus)	7 (7%)	7 (7%)
NAUSEA (nausea, nausea aggravated)	28 (28%)	37 (37%)
POOR APPETITE (anorexia, appetite decreased)	4 (4%)	9 (9%)
SLEEPLESSNESS (insomnia)	6 (6%)	5 (5%)
VOMITING (vomiting)	18 (18%)	27 (27%)
Number of patients reporting any of the above	72 (73%)	78 (77%)

A total of 192 (96%) patients reported continuing a concomitant medication into the double-blind phase. The most common categories reported were laxatives (112 patients), psycholeptics (81 patients) and antacids, drugs for treatment of peptic ulcers and antiflatulants (80 patients). A total of 126 (63%) patients reported starting a medication during the double-blind phase. This high percentage is indicative of the unstable condition of the majority of these cancer patients. The most common category reported was laxatives (49 patients).

Tables 94 and 95 summarise the use of laxatives and anti-emetics ongoing or started during the study. As expected constipation and nausea were some of the most common adverse events reported during the study.

Table 94 Summary of laxatives ongoing or starting during the double-blind phase

	Hydromorphone (n=99)	Morphine (n=101)	Overall (n=200)
Number of patients reporting a therapy[a]	69 (70%)	71 (70%)	140 (70%)
ARACHIS OIL	-	1	1
BISACODYL	5	5	10
CARBOXYMETHYLCELLULOSE SODIUM	1	-	1
CASCARA DRY EXTRACT	2	1	3
CO-DANTHRAMER	2	2	4
COLOPEG	-	1	1
COLOXYL WITH DANTHRON	4	1	5
DOCUSATE	4	2	6
DORBANEX	17	12	29
FLEET ENEMA	4	2	6
GLYCEROL	3	1	4
ISPAGHULA	2	-	2
LACTITOL	-	1	1
LACTULOSE	26	27	53
LIQUIDEPUR	-	1	1
MACROGOL	3	4	7
MAGNESIUM HYDROXIDE	2	4	6
MAGNESIUM HYDROXIDE+LIQUID PARAFFIN	6	2	8
MAGNESIUM OXIDE	1	2	3
MAGNESIUM SULFATE	-	1	1
MINERAL OIL EMULSION	-	1	1
PARAFFIN	1	4	5
PARAFFIN, LIQUID	3	-	3
PHOSPHATES ENEMA	1	1	2
POLYETHYLENE GLYCOL	-	1	1
PSYLLIUM HYDROPHILIC MUCILLOID	1	1	2
SENNA	10	11	21
SENNA+DOCUSATE SODIUM	-	1	1
SENNOSIDES	1	-	1
SODIUM CITRATE+SODIUM LAURYL SULPHOACETATE	-	2	2
SODIUM CITRATE+SODIUM LAURYL SULPHOACETATE+SORBITOL	1	4	5
SODIUM LAURYL SULFATE	1	-	1
SODIUM PICOSULFATE	9	14	23
STERCULIA	-	1	1

[a] not mutually exclusive

Table 95 Summary of anti-emetics ongoing or starting during the double-blind phase

Therapy [a]	Hydromorphone (n=99)	Morphine (n=101)	Overall (n=200)
Number of patients reporting a previous medication	26 (26%)	40 (40%)	66 (33%)
CYCLIZINE	5	8	13
GRANISETRON	3	4	7
METOCLOPRAMIDE	18	30	48
ONDANSETRON	5	1	6
PROCHLORPERAZINE	2	2	4
TROPISETRON	2	3	5

[a] not mutually exclusive

In summary then, for the adverse events reported, there were no statistically significant differences between the treatment groups in terms of the number of patients reporting adverse events either in the IR or CR phases or for both phases combined.

Three patients died during the double-blind study period (patient numbers 78, 94 and 171; all received morphine therapy). Patient number 78, a 68 year old, female Caucasian died following a stroke (cerebrovascular accident) after two days of the morphine IR treatment period. Relationship to therapy was recorded as unlikely. Patient number 94, a 52 year old, male Caucasian experienced rapid progression of disease with physical and mental deterioration and died after five days of the morphine CR phase. Relationship to therapy was recorded as unlikely. Patient number 171, a 20 year old, male Caucasian was found dead after eight days of treatment in the morphine IR phase. The adverse event leading to death was recorded as progressive disease. Relationship to therapy was recorded as none.

Serious adverse events (SAEs) were defined in the protocol as any event that was life threatening or resulted in death, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect or other medically important conditions. SAEs were reported for 23 patients during the double-blind study period (10 in the hydromorphone group and 13 in the morphine group). Twelve patients were withdrawn from the study as a consequence of their serious adverse events (four in the hydromorphone group and eight in the morphine group, including the three deaths during study treatment described above). Summary details are provided in Table 96.

Table 96. Summary of serious adverse events by phase

Patient No.	MedDRA term	Severity	Relationship to therapy	Outcome
IR phase				
Hydromorphone				
2	WEAKNESS	Moderate	None	Ongoing
5[a]	AGITATION	Severe	Definite	Resolved
	MYOCLONIC JERKS	Moderate	Definite	Resolved
	VOMITING	Moderate	Probable	Resolved
264	PATHOLOGICAL FRACTURE	Severe	None	Resolved
303[a]	VOMITING	Severe	Possible	Resolved
363	ASTHENIA	Severe	None	Death[b]
Morphine				
1[a]	HALLUCINATIONS	Moderate	Probable	Resolved
	ABNORMAL DREAMS	Moderate	Probable	Resolved
78[c]	CEREBROVASCULAR ACCIDENT	Severe	Unlikely	Death
171[c]	CONDITION AGGRAVATED	Severe	None	Death
287[a]	CONVULSIONS	Severe	None	Unknown
CR phase				
Hydromorphone				
20	PYREXIA	Mild	None	Resolved
23	PAIN EXACERBATED	Moderate	Probable	Residual effect
170	DIZZINESS (EXC VERTIGO)	Moderate	Probable	Residual effect
	NAUSEA	Moderate	Probable	Residual effect
226	HYPERCALCAEMIA	Moderate	Unlikely	Resolved
	NAUSEA	Moderate	Unlikely	Resolved
255[a]	PNEUMONIA ASPIRATION	Severe	Possible	Resolved
	HYPOTENSION	Moderate	Possible	Resolved
	LOSS OF CONSCIOUSNESS	Moderate	Possible	Resolved
	VOMITING	Moderate	Possible	Resolved
363[a]	DELIRIUM	Severe	Possible	Resolved
Morphine				
6	PLEURAL EFFUSION	Severe	None	Ongoing
	CONDITION AGGRAVATED	Severe	None	Death
22	PULMONARY EMBOLISM	Moderate	Unlikely	Residual effect
29	ABDOMINAL PAIN	Severe	None	Residual effect
	VOMITING	Severe	None	Residual effect
79[a]	METASTATES TO BRAIN	Severe	Unlikely	Death
94[c]	DYSPNOEA	Severe	Possible	Death
	FALL	Severe	Possible	Death
	CONDITION AGGRAVATED	Severe	Unlikely	Death
113	CONSTIPATION	Moderate	Probable	Resolved
115[a]	ILEUS PARALYTIC	Severe	Unlikely	Resolved
	METASTATES TO ABDOMINAL CAVITY	Severe	Unlikely	Ongoing
172[a]	NAUSEA	Severe	Probable	Resolved
	VOMITING	Moderate	Probable	Resolved
212	CONDITION AGGRAVATED	Severe	None	Death
	SOMNOLENCE	Severe	Probable	Resolved
Post-treatment				
81	RESPIRATORY FAILURE (EXC NEONATAL)	Severe	None	Death
255	LEUCOCYTOSIS	Moderate	Unlikely	Resolved

a Withdrawn
b Adverse event started in IR phase, patient was withdrawn because of a serious adverse event in CR phase and subsequently died
c Patient withdrawn because of death in double-blind study period

In summary, then, for deaths and serious adverse events, the proportion of patients reporting events during the study was similar in both treatment groups. Given the severity of the patients' underlying disease state, the occurrence of such events was not unexpected and many were related to the patients' background illness. Around a third (32%) were recorded as definitely or probably related to the study treatment. None of the deaths were considered to be related to the study therapy.

Details of adverse events leading to withdrawal are listed in Table 97. This includes both serious and non-serious adverse events.

Table 97. Adverse events leading to withdrawal by phase

Patient No.	Reason for withdrawal	MedDRA term	Severity	Relationship to therapy
IR Phase				
Hydromorphone				
5	Adverse events	AGITATION[a]	Severe	Definite
		MYOCLONIC JERKS[a]	Moderate	Definite
		VOMITING [a]	Moderate	Probable
18	Adverse events	NAUSEA	Mild	Possible
100	Adverse events	NAUSEA	Severe	Probable
		VOMITING	Severe	Probable
215	Adverse events	PRURITUS	Mild	Probable
		SOMNOLENCE	Moderate	Probable
296	Adverse events	ACCIDENT	Moderate	Probable
		CONFUSION	Severe	Probable
		ECCHYMOSIS	Moderate	Probable
		OEDEMA LOWER LIMB	Moderate	None
		HALLUCINATIONS	Moderate	Probable
303	Adverse events	VOMITING [a]	Severe	Possible
309	Adverse events	MOOD ALTERATION	Severe	Definite
		PERIPHERAL NEUROPATHY	Severe	None
322	Adverse events	VOMITING	Mild	Probable
369	Adverse events	DIARRHOEA	Moderate	Unlikely
Morphine				
1	Adverse events	HALLUCINATIONS [a]	Moderate	Probable
		ABNORMAL DREAMS[a]	Moderate	Probable
42	Adverse events	NAUSEA	Mild	Definite
		VOMITING	Moderate	Definite
		NAUSEA AGGRAVATED	Severe	Definite
78	Death	CEREBROVASCULAR ACCIDENT [a]	Severe	Unlikely
171	Death	CONDITION AGGRAVATED[a]	Severe	None
287	Adverse events	CONVULSIONS [a]	Severe	None
295	Adverse events	SOMNOLENCE	Moderate	Possible
330	Adverse events	CONSTIPATION	Moderate	Probable
		DIZZINESS (EXC VERTIGO)	Mild	Probable
		MYALGIA	Mild	Unlikely
		SOMNOLENCE	Mild	Probable
		VOMITING	Mild	Unlikely
339	Adverse events	SEDATION	Severe	None
		ANXIETY AGGRAVATED	Severe	None
365	Adverse events	CONFUSION	Moderate	Probable
		NAUSEA	Moderate	Probable
		SOMNOLENCE	Moderate	Probable
		VOMITING	Moderate	Probable

a Classified as a serious adverse event
b Onset date post-treatment

Table 97. Adverse events leading to withdrawal by phase (continued)

Patient No.	Reason for withdrawal	MedDRA term	Severity	Relationship to therapy
CR Phase				
Hydromorphone				
147	Adverse events	HALLUCINATION	Moderate	Probable
237	Adverse events	AGGRESSION	Moderate	Possible
		ANXIETY	Moderate	Possible
		CONFUSION	Moderate	Possible
255	Adverse events	PNEUMONIA ASPIRATION[a]	Severe	Possible
		HYPOTENSION [a]	Moderate	Possible
		LEUCOCYTOSIS [b]		
		RESPIRATORY FAILURE (EXC NEONATAL)	Severe	Possible
		LOSS OF CONSCIOUSNESS [a]	Moderate	Possible
		VOMITING [a]	Moderate	Possible
331	Adverse events	ARTHRALGIA	Mild	None
		SWEATING INCREASED	Mild	Possible
363	Adverse events	DELIRIUM[a]	Severe	Possible
370	Adverse events	DIARRHOEA	Mild	Unlikely
Morphine				
79	Disease progression	METASTASES TO BRAIN[a]	Severe	Unlikely
94	Death	CONDITION AGGRAVATED[a]	Severe	Unlikely
115	Disease progression	ILEUS PARALYTIC[a]	Severe	Unlikely
		METASTATES TO ABDOMINAL CAVITY[a]	Severe	Unlikely
172	Adverse events	NAUSEA[a]	Severe	Probable
		VOMITING [a]	Moderate	Probable
212	Adverse events	LOWER RESPIRATORY TRACT INFECTION	Severe	None
		SOMNOLENCE[a]	Severe	Probable
261	Withdrew consent	SWEATING INCREASED	Moderate	Unlikely
		ANOREXIA	Moderate	Unlikely
		OEDEMA AGGRAVATED	Moderate	Unlikely
		FATIGUE AGGRAVATED	Moderate	Unlikely
276	Adverse events	CONFUSION	Moderate	Definite
		DRY MOUTH	Severe	Definite
		INSOMNIA	Severe	Definite
333	Adverse events	VOMITING	Moderate	Possible

a Classified as a serious adverse event
b Onset date post-treatment

Figure 25 presents the Kaplan-Meier estimates for the time to withdrawal (irrespective of study phase) by treatment group. There was no statistically significant difference between treatment groups in the time to withdraw irrespective of phase (p=0.17).

Figure 25. Kaplan-Meier estimates for time to withdrawal (irrespective of study phase)

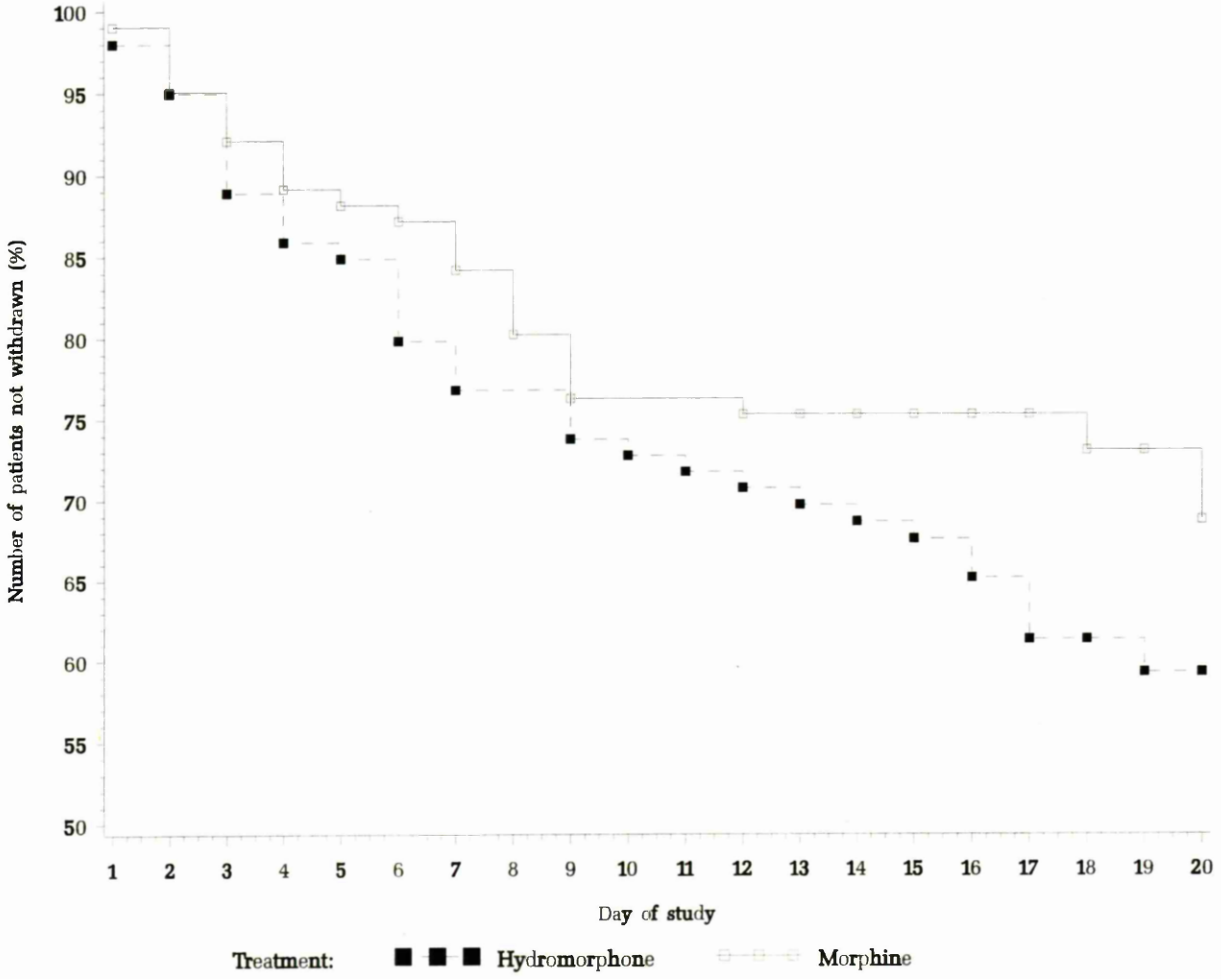


Table 98 summarises laboratory abnormalities which were reported as treatment emergent adverse events. The numbers of patients were similar in each group.

Table 98. Number (percentage) of patients experiencing specific treatment emergent laboratory abnormalities

MedDRA preferred term	Number of patients reporting	
	Hydromorphone (n=99)	Morphine (n=101)
ANAEMIA	4 (4%)	6 (6%)
LEUCOCYTOSIS	-	1 (1%)
LEUCOPENIA	2 (2%)	1 (1%)
NEUTROPENIA	2 (2%)	-
PANCYTOPENIA	-	1 (1%)
THROMBOCYTOPENIA	3 (3%)	-
BLOOD POTASSIUM DECREASED	1 (1%)	-
GLYCOSURIA PRESENT	1 (1%)	-
HAEMATURIA PRESENT	2 (2%)	1 (1%)
HAEMOGLOBIN DECREASED	-	2 (2%)
LABORATORY TEST ABNORMAL	1 (1%)	-
PLATELET COUNT ABNORMAL	-	1 (1%)
PLATELET COUNT DECREASED	-	1 (1%)
PROTEINURIA PRESENT	1 (1%)	-
TRANSAMINASE INCREASED	-	1 (1%)
WHITE BLOOD CELL DECREASED	-	1 (1%)
WHITE BLOOD CELL INCREASED	-	1 (1%)
HYPERCALCAEMIA	1 (1%)	1 (1%)
HYPOKALAEMIA	-	1 (1%)

In conclusion, the overall tolerability of hydromorphone was comparable with morphine.

5.4.6 Discussion

It is generally acknowledged that controlled studies in cancer pain are difficult to conduct owing to the potentially confounding factors associated with the seriousness of the disease state, high withdrawal rate and the effects of the many concomitant medications required by the patients. This study is therefore unique, being the first international, multicentre, phase III, randomised, double-blind, parallel-group study, involving a complex multiple ascending dosing schedule, to successfully assess the equivalence of efficacy between hydromorphone (IR and CR) and morphine (IR and CR). The investigators' ability to titrate dose to effect within the design of the study meant that the particular doses selected would not interfere with the outcome of the study. These dose levels were selected on the basis that oral hydromorphone is five-times more potent than morphine, within the constraints imposed by available dose strengths. The element of dose titration within the study also allows an estimate of equipotency to be derived from the exposure data gathered. Thus, the mean amount of milligrams consumed per day of 28.0 for the hydromorphone group and 129.0

(1:4.61) for the morphine group in the IR phase and 35.4 for the hydromorphone group and 151.8 (1:4.29) for the morphine group in the CR phase. When the mean dose per day at the end of the CR phase is used, the value is 1:4.32. This suggests that a factor of between four and five is appropriate to use when calculating equipotency.

Eleven-point pain scales have been shown to be effective measures in studies of chronic pain patients (Jensen 1999). "Worst pain" was specifically chosen as the primary variable for assessing efficacy in this study, since there is evidence to suggest that it is this most intense pain that patients experience which interferes most with daily life activities (Daut 1983). Of all the parameters assessed in the BPI, "worst pain" is also the most sensitive measure in the clinical study setting (Cleeland 1994b, Mendoza 2001b). This certainly seems to have been the case in this study, where "worst pain" was the only measure with sufficient sensitivity to detect a statistically significant difference between the treatment groups.

In order to ensure that the study was adequately powered, the protocol made provision for the variability of the principal measure to be re-estimated during the study. The original sample size was approximately 70 patients per treatment group assuming a variability of 2.0 for the primary efficacy variable. After 55 patients had completed the study, the revised estimate was 2.24 for the IR phase and 2.50 for the CR phase. Based on these data, the sample size was increased to 82 patients per group to be randomised into the study. A further re-estimation of variability for the CR phase was performed after 120 patients had completed the study. This estimate was 2.7 and the sample size was increased to 100 patients per group to be randomised. It was subsequently concluded that the study precision was adequate to meet the objectives since the actual variability for the principal measure of efficacy for the CR phase (2.46 for the "full analysis" set and 2.25 for the per-protocol set) was less than the estimated value.

The two treatment groups were balanced at entry for demographic and baseline variables of BPI "worst pain" in the past 24 hours, ECOG performance status and nature of predominant pain. The mean baseline values for "worst pain" scores was 6.3 on an 11-point scale, which was comparable to those seen in other cancer pain studies such as Paice, 1998 where the mean value was 6.99. These scores equate with moderate to severe pain (Serlin 1995).

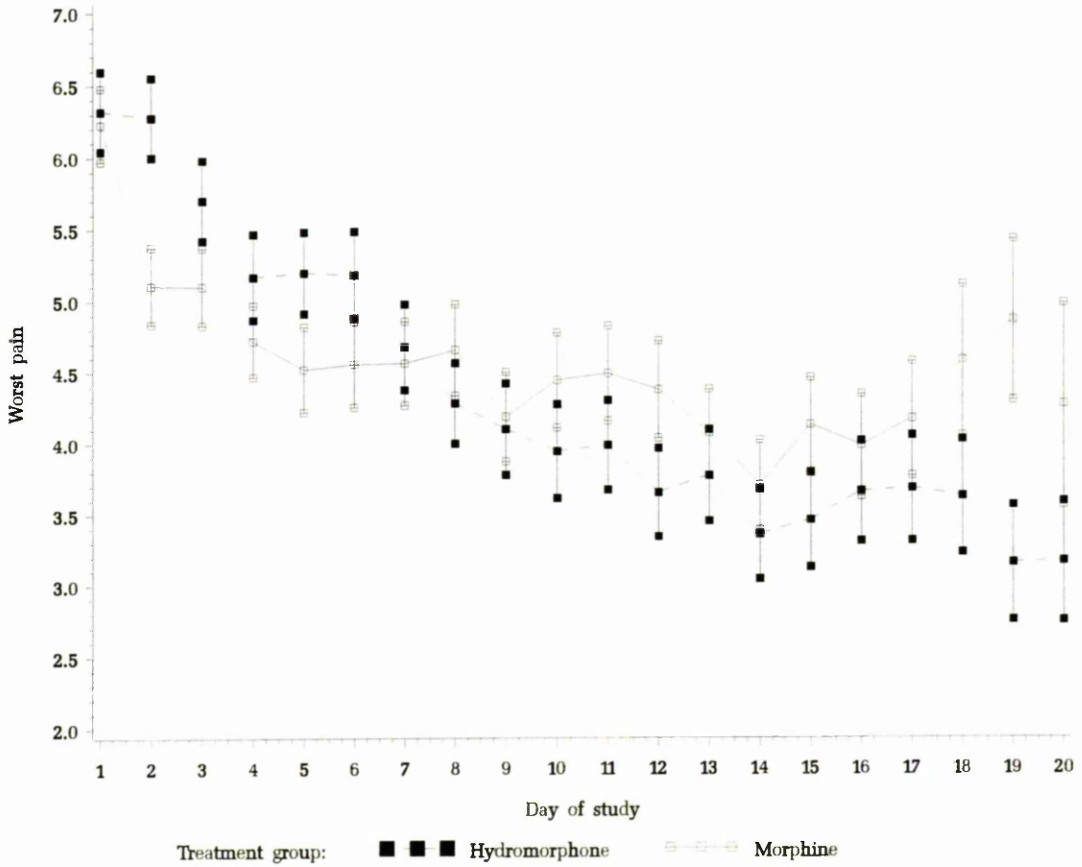
Completion rates for both phases of the study were high (82%), with an overall completion rate of 67%. The withdrawal rate in the CR phase of the study was comparable to that seen in published data where patients had been titrated to pain control prior to randomisation (O'Brien 1997; Broomhead 1997; Moriarty 1999) but greater than those seen in a longer (30 days) crossover trial reported by Ahmedzai (1997).

Table 99. Completion rates in comparable studies

Study	Duration of treatment (days)	Completion rate (%)
DO118	11	133/163 (82%)
O'Brien 1997	14	69/85 (81%)
Moriarty 1999	6	89/100 (89%)
Broomhead 1997	7	152/172 (88%)
Ahmedzai 1997	30	110/202 (54%)

The results of the study showed that there were decreases in "worst pain" in both treatment groups, confirming the basic efficacy of the two treatments under the study conditions (see Figure 26).

Figure 26. Mean profile with standard error bars for "worst pain" during the whole of the study (observed data – "full analysis" set)



NB. The increase in scores seen at the end of the sampling time is a function of the cohort data. The mean number of days in the study was 14.4 and the plot extends to 20 days. In general, patients remaining in the study for longer periods were those experiencing more difficulties with pain control.
The increase in the error bars at the later time points is explained by the same phenomenon.

According to the protocol, treatment with hydromorphone was to be considered equivalent to morphine if the 95% two-sided confidence interval for the difference between the adjusted means for the principal measure of efficacy ("worst pain" score of BPI in the past 24 hours) lay within -1.5 to 1.5. For the IR phase this was true and therefore hydromorphone IR was proven to be equivalent to morphine IR. For the CR phase the lower limit of the 95% confidence interval was less than –1.5 which implied that the superiority of hydromorphone could not be disproved. However, the upper limit was less than 1.5 and therefore non-inferiority of hydromorphone was proven. Furthermore, there was a statistically significant difference between the treatment groups in favour of hydromorphone for the CR phase for both the "per protocol" and the "full analysis" sets (p=0.046 for the "full analysis" set and p=0.049 for the per-protocol set).

The dose levels at which patients reached dose stable pain control were similar in the two treatment groups, suggesting that the packaging of the six dose levels of the respective treatments were well matched.

For the secondary efficacy variables there were no statistically significant differences between the treatments (i.e. other BPI variables, ECOG, Mini-Mental state), except for how pain had interfered with normal work at the end of the IR phase where hydromorphone was favoured (p=0.046), but this is probably just an artefact of multiple testing. There was also a trend in favour of hydromorphone for "pain now" p.m. at the end of CR phase (p=0.09). The most likely explanation for this finding is that measurement of this variable coincided with the period of sustained higher plasma concentrations characteristic of the hydromorphone CR formulation (Knoll Pharmaceutical Company study D-101; Knoll Pharmaceutical Company study DO108; Knoll Pharmaceutical Company study C-96-054-01), whereas plasma concentrations of morphine from the twice-daily administered CR formulation would have been at trough levels. Additionally, it has been remarked that for some patients, existing twice-daily formulations require three-times-daily administration in order to maintain plasma levels sufficiently (Hanks 2001). This observation would increase the chance of a "trough effect" being of clinical relevance. Another possible explanation for the lower pain scores for the hydromorphone treatment group in the CR phase is improved compliance. Patients with chronic cancer pain are not generally regarded as being poor medicators, but some reports from other therapeutic areas suggest that a once-daily

formulation will result in more accurate use of medication, compared with twice-daily formulations (Bloom 2001).

There were some interesting differences between the two drugs in the IR phase. Firstly, time to dose stabilization was statistically significantly longer in the IR phase for hydromorphone than morphine IR (6.5 days verus 5.2 days). Second, the higher rates of patients reporting adverse events in the hydromorphone treatment arm during the IR phase (67 versus 60% for morphine), which contrasted with the lower rates in the SR phase (79 versus 87% for morphine). Thirdly, the higher dropout rates for the hydromorphone group in the IR phase (22 versus 15% for morphine). And lastly, the use of breakthrough pain medication was statistically significantly higher for the hydromorphone group in the IR phase. These may be explained by the fact that almost a third of the patients used morphine prior to starting the study. In order to explore this possibility, these parameters were examined using only those patients who were receiving morphine prior to the start of the study. The findings are shown in Table 100.

Table 100 Time to dose stabilisation, adverse event reporting, reason for withdrawal and use of breakthrough medication – all in IR phase only

	Morphine pre-treatment population		Full study population	
	Hydromorphone	Morphine	Hydromorphone	Morphine
n	32	36	99	101
Time to: dose stabilisation				
n (%)	66%	78%	74%	80%
Δ n (%)	12		6	
Mean time (days)	7.2	5.7	6.5	5.2
Δ time (days)	1.5		1.3	
Adverse events				
% reporting	75%	53%	67%	60%
Δ % reporting	22		7	
Reason for withdrawal				
n (%)	31%	19%	22%	15%
Δ n (%)	12		7	
Adverse events	6	2	9	7
Lack of efficacy	2	1	6	1
Protocol violation	1	1	3	1
Withdrawal of consent	1	3	3	4
Administrative reasons	-	-	1	-
Death	-	-	-	2
Use of breakthrough medication				
n (%)	61%	53%	65%	54%
Δ n(%)	8		11	
Mean no. doses	1.9	1.5	2.1	1.4
Δ no. doses	0.4		0.7	

In general, this supports the possibility that pre-treatment with morphine biased these results, since the differences between the treatment groups were more in favour of the morphine group in the subpopulation that was already receiving morphine at the time of randomisation. The exceptions to this general trend was in use of breakthrough medication and the number of patients withdrawing due to lack of efficacy, in which the morphine treatment group was relatively less favoured in the morphine-pretreated subpopulation. Overall, then, this suggests that the IR dose titration part of the study allowed the morphine-prior-treatment-factor to be accommodated for, following which the CR treatment phase proceeded with a final outcome in favour of hydromorphone CR.

In the CR phase, the withdrawal rate was also greater for the hydromorphone group (22%) compared with the morphine group (15%). This finding is difficult to account for, given that

the other measures made in this phase suggest at least parity (the secondary measures of efficacy) or in some cases (the primary efficacy endpoint and adverse event reporting), superiority of the hydromorphone once-daily treatment.

The overall safety profiles of the two treatments were generally similar and there were no statistically significant differences between the treatments for the proportion of patients reporting adverse events. Despite the high incidence of adverse event reporting in the treatment of pain with opioids in the cancer pain setting, published studies have indicated that overall, patients still attain benefit from these therapies (Savage 1999, Sjogren 2000) and the active management of these side effects is well described (Portenoy 1994). The number of adverse events reported during the morphine IR phase was higher than that reported in published data (Broomhead 1997). The number of adverse events reported in the hydromorphone IR phase was greater than for the morphine IR phase. The longer duration of the IR phase for hydromorphone-treated patients may account for this difference.

Effective treatment of cancer pain is a balance between pain control and adverse events (Portenoy 1994). In this study, the dose levels at which patients reached adequate pain control were similar in the two treatment groups and comparable (129 mg per day in IR phase and 151.8 mg per day in CR phase) to another published study in cancer pain where the daily CR morphine dose was 138 mg (Broomhead 1997). Further, the pain scores being reported at the completion of the CR phase (adjusted means 3.5 and 4.3 for hydromorphone and morphine, respectively) correspond to mild pain (Serlin 1995), in contrast to the moderate to severe pain recorded at the time of randomisation.

The nature of the adverse events reported during hydromorphone and morphine therapy was generally typical of the events associated with these treatments (Paice 1998, Moriarty 1999). There were some numerical trends suggesting more events overall in the morphine treatment group, more constipation and diarrhoea in the hydromorphone treatment group and more nausea and vomiting in the morphine group, but none of these differences appeared to be statistically significant. Regarding the gastro-intestinal adverse events, laxative use appeared to be equal in both groups (70% of patients reporting use in both groups), whereas anti-emetic use was greater in the morphine treatment group (40% of patients) than the hydromorphone group (26% of patients).

Most of the adverse events in the study were mild or moderate in severity and around half were recorded as being of unlikely or no relationship to therapy. The higher number of withdrawals in the hydromorphone group in the CR phase of the study is difficult to explain but was not statistically significant.

The occurrence of three deaths during the study, together with a further 17 patients who experienced serious adverse events was not unexpected, given the severity of the patients' conditions and the progressive nature of the disease. None of the deaths were considered to be related to the study therapy. Many of the serious adverse events tended to be associated with the underlying disease, although a proportion (32%) were considered to be definitely or probably related to the study treatment.

5.4.7 Conclusions

Despite the complexity of the study design and the known difficulties associated with the management of cancer patients, the results of this study clearly demonstrated equivalence for "worst pain" between hydromorphone IR and morphine IR. For the CR treatments, the superiority of hydromorphone to morphine could not be disproved; however, non-inferiority of hydromorphone to morphine was proven and there were statistically significant differences in favour of hydromorphone for the CR phase. From examining the secondary efficacy measures to try and find an explanation for this finding in the CR phase, it would appear to be related to the difference in "pain now" reporting at time of trough plasma levels, suggesting a superior controlled-release performance of the hydromorphone CR formulation. There are no other studies published in cancer pain where one opioid/formulation has demonstrated a superior mean pain score over another.

The safety profiles of the two treatments were comparable, although numerical trends and concomitant medication use suggested some possible advantages of one drug over another, although these were not statistically significant.

Overall, hydromorphone CR provides a convenient, once-daily treatment for cancer pain patients which offers superior pain control compared to twice-daily morphine.

6. Overall discussion

6 Overall discussion

This thesis is presentation of a segment of a large body of work undertaken over 5 years with a budget running to several million pounds. Clearly, this size of project could not be undertaken by one individual but instead, depends on a team approach involving many disciplines. The role of the author in this process was continuous and pivotal, since the only medical input to the project from within the company was from the author. In addition, the author had responsibility for the key activities of seeking expert opinions, reviewing literature data and the design, conduct, analysis and reporting of separate studies. Most importantly, the author had overall responsibility for the entire clinical programme, including its budget, and was held responsible by Knoll for this. The amount of data produced by the project far exceeds what could be condensed into one thesis. Therefore, the approach taken was to concentrate on the three clinical studies that the author was most closely involved with and limit the degree of detail used to deal with other parts of the project.

On first inspection, the area of pain management with opioids may be regarded as an area that has been well characterised through decades of study and well supplied with various agents and formulations for the treatment of patients. On closer inspection, however, there are gaps in the armamentarium of both knowledge and treatment options. The work reported here begun with the premise that a new range of formulations of an existing opioid would add significantly to the useful treatment options available to doctors in Europe. Within this general scope, some important gaps in the information regarding pain management were identified. One of these was the period following parenteral opioid PCA treatment for moderate to severe postoperative pain and the other was the need for prospective, double-blind, randomised, controlled data in the setting of chronic cancer pain. As such, the clinical programme of studies was devised that could achieve registration of the range of formulations for hydromorphone and within this aim, collect data that would add significantly to available knowledge on postoperative acute pain and chronic cancer pain.

Hydromorphone is a far less well established opioid in Europe than morphine. This is less so in the USA where it has been consistently marketed by Knoll since the early part of the last century and is now available through several companies in the USA. Of the different marketed brands of hydromorphone available in the USA, Dilaudid is the most established –

so much so that it gets mentioned in current medical "soaps" such as "ER"! The difference between the two continents in the perception of hydromorphone is presumably attributable to the differences in the ways that the product has been promoted by Knoll over the bulk of the last century. Comparing hydromorphone with morphine from first principles would lead to the conclusion that it is surprising that it is morphine and not hydromorphone that is the more accepted product. Hydromorphone is the more water soluble of the two (Martindale 1993), it is more potent and from the limited information available on metabolites and their pharmacological actions, hydromorphone would appear to present a simpler profile with the lack of a pharmacologically active 6-glucuronide metabolite. The greater water solubility results in the opportunity to create more potent parenteral formulations. This has limited applications, however, given that infusion volumes are only of any practicable consequence in the setting where relatively large doses are required for patients where there is limited subcutaneous mass to receive the infusion. This can be the case in palliative care patients. A possible economic advantage could be made of the smaller infusion volumes possible through the reduced need for changing infusion syringes for devices such as PCA pumps. The economic forces and the technology itself are relatively recent phenomena, however, and are too recent to have affected the relative status of the two compounds. The greater potency on a milligram-per-milligram basis is also of a rather academic interest, since there are no demonstrable benefits in this increased potency other than possible issues regarding volume of administration as described above. The possible advantage of the less complicated metabolite profile has not become a major practical issue, since there is a lack of consensus regarding the problems that the active morphine-6-glucuronide causes. Additionally, both compounds share a 3-glucuronide metabolite and the activity of the hydromorphone-3-G has not been well characterised in the literature.

The recent pharmacokinetic studies of hydromorphone reviewed from the literature present an uncomplicated picture of the molecule. In both formulations, it exhibits dose proportionality and age and sex have little clinically relevant effect on the pharmacokinetics. The oral bioavailability is less (18.7%) than previously reported (50.7%), but is similar to current estimates for morphine (29.2%, Hasselstrom 1993). The reduced oral bioavailability figures are attributed to the assay methodology in the older studies being less able to differentiate parent drug from metabolites. The figure for oral bioavailability that was quoted previously was at odds with pharmacodynamic data which suggested a ratio of 0.2 when comparing parenteral and oral doses (Houde 1986). The revised oral

bioavailability figure is in agreement with these estimates from pharmacodynamic studies. Another feature of the improved sensitivity and selectivity of current hydromorphone assays is the characterisation of a long terminal elimination half-life (15 hours, Durnin 2001b), compared with the value quoted in the literature (2.36 hours, Parab 1988). This new value is derived from a subset of healthy volunteers where it was possible to calculate the terminal elimination half-life. In those where a secondary peak occurred, it was not possible to make a good estimation of this. The clinical relevance of this longer terminal elimination half-life seems to be limited, however, since it only applies to relatively low plasma concentrations (around 10% of Cmax) that have no significant clinical effect. The secondary peaking in plasma levels referred to above may be attributable to hepatic recirculation of drug and metabolite. From the food effect study, there appears to be an interaction taking place (30% increase in AUC and 25% decrease in Cmax) which, again, is similar to findings for morphine (Gourlay 1989). The clinical significance of this finding is limited, however, since the effects on Cmax are unlikely to be of significance to a patient who is well enough to ingest a high fat meal. In terms of the effects on total bioavailability, again, a significant clinical consequence is hard to envisage since other factors occurring during a 24-hour period would have effects on the degree of pain control experienced. In respect to effects of renal and hepatic impairment, the results would have been expected from the knowledge of the pharmacokinetic properties of hydromorphone and its 3-glucuronide. The implications of the effects of increased bioavailability of the parent compound are clear, but for the 3-glucuronide, this is more open to debate, since the effects of what is generally ascribed to be an inactive metabolite are a matter for discussion (Smith 2000). The clinical relevance of the metabolite would appear to be restricted to patients receiving relatively high doses, however. In summary, the current picture of hydromorphone immediate-release pharmacokinetics is very similar to that for morphine.

The sustained-release formulation of hydromorphone clearly achieves a very flat plasma level profile with release of drug from the formulation apparently continuing for up to 24 hours after administration and with an oral bioavailability comparable with the corresponding dose in the immediate-release formulation. Food had little clinically relevant effect on the pharmacokinetics of the sustained-release formulation.

All three of the main clinical studies were positive, which was a great relief to all concerned. One might have thought that embarking on a programme of studies for an

established product would present few hurdles. In practice, however, many analgesic studies have negative outcomes and making an analgesic model work three times without fail is a noteworthy achievement (Schachtel 1991). It is theoretically possible to achieve a positive outcome using an equivalence methodology by running a bad study (Djulbegovic 2001). For example, if the test and control treatment are both inefficacious, then they may still be equivalent according to the statistical definition. One method to address this issue is to include a sensitivity analysis within the equivalence methodology. Incorporating a placebo arm in the study usually does this and a statistically significant difference between the placebo treatment and the active(s) is the proof of sensitivity. The problem with applying this to pain studies of anything other than a short duration comes with the ethical difficulties of placebo treatment. We encountered significant problems with ethics committees even with the single-dose study where the study period was of six hours' duration and immediate rescue therapy was available. Added to this is the regulatory authorities' insistence that the primary efficacy measure must be pain itself and not surrogates such as the use of rescue medication. In the equivalence studies included in this thesis, the proof of efficacy of test and control treatment arms comes from the reduction in pain scores during the study period. In the chronic cancer pain study, this is clearly demonstrated in Figure 22 where the pain scores are seen to diminish with both treatments during the study period. Given that the chronic pain stimulus is assumed to remain relatively constant for the duration of the study and that no other opioid therapies are permitted, this is the proof of efficacy in this trial. For the multiple-dose postoperative study, the pain scores were also seen to have diminished during the study phase (Figure 15) when no analgesic therapy other than test/control was available to the patients. However, in this case, it could not be assumed that the pain stimulus was constant through the study period. Additional proof of efficacy is provided, however, by the statistically significant difference in dose response between the 2-mg and the 6-mg dose level (mean difference 1.1, 98.3% CI 0.1,2.0). Another possible problem with the conduct of equivalence studies is lax conduct allowing many protocol deviations, which results in both treatments being declared equivalent simply through the process of regression towards the mean. This factor is tested for in the analysis of two datasets within each study. The first is the "full analysis" or "intent to treat" dataset and the second is the "per protocol" dataset. In both studies, both analyses produced the same result, thus confirming that study conduct was sufficiently rigorous. Thus, one can conclude that the two equivalence studies certainly were also positive in their outcome.

The selection of the primary efficacy endpoint for the chronic cancer pain study was straightforward, since there were published reports to suggest that "worst pain" was the most clinically relevant and we were advised that it was also the most sensitive in a clinical trial setting (see section 5.4.6). The results of the study confirmed these earlier findings such that the primary efficacy variable was the most sensitive measure. For the postoperative studies, however, there was a conflict between what was perceived to be the more clinically relevant endpoint, pain on movement, and the suggestion from the literature that opioids were more effective with pain at rest (Rainer 2000). The conservative approach was taken, but in retrospect, the pain on movement seems to be the more sensitive measure, since there were more statistically significant differences compared with placebo with this measure (see section 5.2.5.1). The findings from the majority of the secondary efficacy parameters seem to bear out that pain itself is the most sensitive measure in analgesia trials and that the greater the pain level recorded, the greater the chance of demonstrating statistically significant differences.

The selection of the clinical equivalence zone (±1.5 on the 11-point numerical scale) has been described in sections 3 and 5.3.2. On inspection of the data from the two equivalence studies, in retrospect, a range of ±1.0 would have been easier to explain the findings from the studies. In the case of the multiple-dose postoperative study, this range would have resulted in inferiority being declared for the 2-mg dose, equivalence for the 4-mg dose and superiority for the 6-mg dose on the basis of the "pain at rest" scores from either the "per protocol" or the "full analysis" set. In the same study, had "pain on movement" been used, then both the 2 and 4-mg doses would have been declared inferior and the 6-mg dose would have been equivalent. These results would have fitted more conveniently with the findings from the single-dose study, namely that the 2-mg dose was not statistically significantly different from placebo whereas the 4-mg dose was. The apparent difference between the efficacy of the 2-mg dose in the single-dose versus the multiple-dose study may be due to several factors. First, although the SPID value for the 2-mg dose was not statistically significantly different from placebo for pain at rest or on movement, the plot for mean pain score at rest was lower for the 2-mg dose and although this was only transitory for the pain on movement plot, the value at one hour post-dose was statistically significant. Also, results between two studies, even if they are identical, will not always agree. Finally, the flexible dosing regimen in the multiple-dose study meant that the patients in the 2-mg dose received doses more frequently than the 4-mg group. The respective median dosing intervals were

5.6 and 6.6 hours. For the chronic cancer pain study, the results would have been the same as those for the ± 1.5 value, namely that equivalence would have been declared for the immediate-release phase, but superiority of hydromorphone for the SR phase, irrespective of whether the "per protocol" or the "full analysis" data set were used.

The two postoperative studies were very similar in design and shared many common features such as study centres and study procedures. One of the significant differences between the studies related to the baseline qualifying pain score included in the multiple-dose study. The effect of this was that the mean value for pain at rest in the single-dose study was 4.4 whereas for the multiple-dose study it was 5.8. In retrospect, including a qualifying baseline score in the single-dose study would have probably improved the sensitivity in the single-dose study (Averbuch 2000).

The withdrawal rates in the two postoperative pain studies varied across countries, and there appeared to be some consistency between the two studies in this respect. The rates of study completion for the single-dose study in the UK, France and the Netherlands were 53%, 88% and 47%, respectively, with the respective figures for the multiple-dose study being 64%, 79% and 52%. As one would expect, the number of withdrawals due to lack of efficacy was greater in the placebo controlled study (34%), compared to the active control one (17%). Another factor that varied consistently between countries across the two studies was the duration of the PCA. In the single-dose study, the median duration (in hours) was 39.0, 20.3 and 21.0 respectively for the UK, France and the Netherlands. The corresponding figures for the multiple-dose study were 35.2, 21.1 and 20.0, respectively. The centres that took part in each study were not the same for both studies, but from the 24 involved in the single-dose study and the 27 involved in the multiple-dose study, 12 were common to both. These are examples of important factors in clinical trials that cannot be controlled for between centres and countries in the setting of a multicentre, international study.

The single-dose study in acute pain confirmed the findings in the published literature that oral doses of hydromorphone are statistically significantly superior to placebo. In contrast to the published literature, however, it was not possible to discern differences in tolerability between the hydromorphone doses tested.

In the acute pain setting, the single-dose study demonstrates an increase in efficacy when the single dose increased from 2 to 4 mg, but not from 4 to 6 mg. The most obvious and simple explanation is that the 100% increase between 2 and 4 mg was sufficient to distinguish a difference, but the 50% increase from 4 to 6 mg was not sufficient. This study was originally designed to evaluate 2, 4 and 8-mg doses, but theoretical concerns (based around the interpretation of equipotency figures) from a regulatory authority about the safety of the 8 mg dose prevented its use. The dose-responsiveness observed in this study mirrors that described in the published studies of parenteral doses reviewed in section 4.2.2.2.

In the setting of the multiple-dose acute pain study, 2, 4 and 6 mg were not distinguishable in terms of their therapeutic equivalence to morphine 20 mg. These findings are in general agreement with a small published study comparing hydromorphone with morphine (Turek 1987). The three dose levels selected were distinguishable by the mean pain scores that they attained. The lack of a difference in the equivalence outcome between 2 and 4 mg was partly attributable to an increased frequency of dosing in the 2-mg dose group, compared with the 4-mg dose group. This is an inevitable consequence of a flexible dosing regimen, which was in turn a requirement of caring for a group of patients in the post-operative setting over an extended period. In summary, 2-mg doses of hydromorphone IR can be effective in the acute pain setting, but a more reliable response is obtained from a 4-mg dose.

The onset and duration of action of single oral doses of hydromorphone from the single-dose, placebo controlled trial are in general agreement with the published data reviewed in section 4.2.2.3.4. However, the onset of action, which would appear to be within one hour, is somewhat earlier than would have been expected from some of the literature data. It is, however, in agreement with the pharmacokinetic data from recently published studies (Durnin 2001a, b, c, d, e, f). Also, the duration of action from the single-dose study (from the analysis of time for pain to return to baseline score) would appear to be between three and four hours, rather than the longer durations quoted in some of the references.

The "Gold Standard" reference therapy for strong opioids is clearly morphine and this was the comparator used in both the multiple-dose acute pain study and the chronic pain study. The comparative multiple-dose study in postoperative pain has established statistically that

hydromorphone is within the efficacy range of morphine, which is the "global standard" in moderate to severe pain. In this study, for all three dose levels when dosed on a flexible "3-hourly as required" basis, therapeutic equivalence was demonstrated. The key to equal efficacy with all opioids is, of course, the equipotency ratio used to calculate doses for comparison. For this study, a ratio of 1:5 was expected to be the outcome and indeed, the value was calculated as being between 1:4 and 1:5, depending on the dataset used ("intent to treat" or "per protocol") and the measure of pain used (pain at rest or pain on movement). For the cancer pain study a ratio of 1:5 was again used for the calculation of doses of the respective medications. Using the daily dose of each respective treatment at the end of the SR phase and not taking rescue medication into account (since the use of this was very similar between the two treatment groups); the equipotency value worked out to be 4.32. These data suggest more consistency than those published in the literature, which vary from two to 10. One specific concern raised from the literature is the possibility that the existing dose conversion ratios were predominantly based on single-dose data, citing a paper where dosing for 13 days had produced a value of 3:1, in contrast to the 7:1 value obtained at the start of dosing (Dunbar 1996, Anderson 2001). The data from the cancer study in this thesis arise from a mean dosing period of 16 days; therefore, this argument would not appear to be valid.

In the comparative chronic pain study, patients were titrated to dose-stable pain control in both IR and CR phases of the study and assessed for equivalence of efficacy using items of the BPI. This study demonstrated the clinical equivalence of efficacy between hydromorphone and morphine in the IR phase of the study whilst the superiority of hydromorphone could not be disproved in the CR phase. This finding is consistent with the published study by Moriarty (1999) which found hydromorphone to be as effective as morphine in the treatment of chronic cancer pain.

Patients receiving morphine (the comparator treatment) prior to baseline probably affected both of the equivalence trials. In the case of the multiple-dose postoperative study, this was an inevitable consequence of the study design. All patients were receiving morphine parenterally prior to randomisation. In the cancer pain study, about one third of patients were receiving morphine prior to randomisation. One would expect this to have at least some effect on the outcome of the two studies. In the case of the postoperative study, at the time of randomisation, all patients should have had their pain satisfactorily controlled. An

element of selection could have occurred in the PCA part of the study, whereby those patients who did not tolerate morphine well dropped out of the study, leaving a selected group of "morphine responsive" patients. It is, unfortunately, not possible to explore this issue, since data was not collected in the PCA part of the study in such a way as to enable this withdrawal phenomenon to be well characterised. Therefore, the subset of patients continuing to randomisation to the morphine treatment arm remained on morphine, except that it was administered by a different route. One would anticipate that this group would follow a smoother clinical course than those in the hydromorphone treatment arms who had to become accustomed to a new agent. In the case of the cancer pain study, another factor would have come into play. Patients could enter this study irrespective of their current pain control and there was no stabilisation period prior to randomisation. For those patients already receiving morphine and enjoying good pain control, one would expect them to fare better if they were randomised to continue to receive morphine. On the other hand, those having problems with morphine could be expected to fare better if they were allocated hydromorphone, on the theoretical basis of receiving benefit from opioid "switching" (Bruera 1996). Unfortunately, the patients' current status on existing therapy was not well documented in the cancer pain study, so it is not possible to identify which group each patient would fall into. The data from the initial IR phase would suggest, however, that the former was more often the case, since the hydromorphone treatment group exhibited longer times to pain stabilisation and more adverse event reporting (see section 5.4.6).

The adverse event data from the single-dose postoperative study was remarkable for not being able to distinguish between active and placebo doses. Thus, even for a drug like hydromorphone with a well known side effect profile, it was possible to administer single efficacious doses without any apparent change in adverse event reporting.

The safety data from the multiple-dose study in patients with acute postoperative pain makes a direct comparison between hydromorphone IR and morphine and finds no statistically significant difference. There appear to be some differences in reporting rates of, for example, nausea, in morphine's favour, but very large numbers of patients would need to be studied to demonstrate statistical significance. Similarly, in the cancer pain study, no statistically significant differences were found between the treatments in terms of safety parameters. What appeared to be a possibly important trend in the postoperative data concerning apparently higher rates of nausea with hydromorphone compared with morphine

were not mirrored in the cancer pain study. In fact, the trend was in the opposite direction in the cancer pain study. The nature of the adverse events reported during hydromorphone and morphine treatment in the cancer pain study was generally typical of the events associated with these treatments as reported in the published literature (Paice 1998, Moriarty 1999).

The main focus regarding safety parameters centred on adverse events, serious adverse events, deaths and withdrawal rates. Additional inspection of the data for less common, but more significant events failed to suggest any safety concerns. Clearly, a significant element in the consideration of safety in respect to hydromorphone is its extensive use in North America for most of the 20th century. The published data on the use of hydromorphone makes many comparisons with other opioids and although individual studies identify differences in specific safety measures, the general picture is of the comparability, rather than the difference of hydromorphone compared with other opioids. An important issue regarding the reporting of safety data from clinical trials is the power of the comparisons being made. In fact, none of the studies in this thesis are sufficiently powered to detect differences in reporting rates. Sample sizes far larger even than these relatively large studies are required to make a true assessment of these differences (Edwards 1999). For a hypothetical case of a treatment which causes an adverse event at a rate of 40% and a comparator treatment with a corresponding rate of 30%, in order to achieve 90% power at a 5% significance level, 492 patients would be required for each treatment group.

The incidence of adverse event reporting varied greatly between the single and multiple-dose postoperative studies. For opioid-related events, either ongoing or occurring after randomisation, the total number of patients reporting in treatment groups in the single-dose study were between 14 and 27%. This contrasts with 42 to 61% in the multiple-dose study. This provides dramatic evidence of the difference in reporting rates caused by increased dosing and longer observation periods in a similar setting and patient population.

Respiratory depression is clearly a direct pharmacological action of opioids, including hydromorphone. In the treatment of chronic pain, this is generally of less concern since doses can be titrated gradually and patients are ambulant. The more immediate concern is in the acute pain setting and this concern had an effect on the programme of studies when one regulatory authority questioned the use of an 8-mg dose of hydromorphone in the single dose postoperative pain study. In response to this concern, the dose was subsequently

reduced to 6 mg. The results of both postoperative pain studies, however, were that there were no reports of respiratory depression.

One pharmaco-epidemiological study involving hydromorphone has been published. Miller's publication (Miller 1980) was of a prospectively collected series of cases from 22 hospitals over 12 years where parenteral narcotics were used. Although Miller points out that hydromorphone was administered to patients with a higher fatality rate, longer duration of hospital stay, higher diagnosis rate of neoplasm and for a longer duration of exposure, he concludes that these factors are not sufficient to account for a higher adverse event reporting rate for hydromorphone. The total proportion of patients reporting adverse events for hydromorphone was 18.3%, compared with 5.8% for morphine. The sample is further distorted however, by another two factors. The first relates to sample size; 1821 received morphine and 115 received hydromorphone and secondly, morphine was substantially used for pre-medication and as a treatment for heart failure, bronchospasm, anxiety, angina and "numerous other indications", whereas hydromorphone was used exclusively for pain. It is hard to reconcile the findings of this study with the numerous controlled comparison of hydromorphone with other opioids. The numerous factors that weaken the comparison in this study may account for a large part of the difference observed.

The conduct of both postoperative pain studies was relatively straightforward in respect to centre selection and the recruitment phases. Both of these studies completed the recruiting of patients more quickly than expected. The single-dose study completed recruiting 200 patients in five months, while the multiple-dose study recruited 270 patients in nine months. In contrast to these studies, consultants warned from the very early stages of planning the cancer pain study that recruitment would be a big problem (Jordhoy 1999, Hardy 2000). This certainly was the case, with recruitment of 200 patients taking nearly two years, despite the involvement of eight countries and more than 30 centres. This study also needed adjustment to inclusion criteria made in order to attempt to boost recruitment. In making these changes, the concern is always that by making selection criteria less strict, the quality of the study will suffer. Fortunately, the integrity of the study was not adversely affected, however.

7. Overall conclusions

7 Overall conclusions

Hydromorphone is undoubtedly a strong opioid. It has been shown in clinical practice and clinical studies over the last 30 years and up to the present date, to be within the range of potency, efficacy and safety of other strong opioids such as morphine. It is well accepted that there are significant variations in individual patients in the response of one opioid compared to another (McQuay 1999), particularly in relationship to adverse side effects as well as efficacy. Publications support the beneficial effects of transferring patients from one opioid to another if they have either not responded or suffered severe side effects (de Stoutz 1995).

The range of efficacy and potency of hydromorphone in the acute pain, as well as the chronic pain studies has addressed moderate to severe pain. On this basis, it is appropriate that hydromorphone will be indicated for the management of moderate to severe pain. The safety data are within the same range as other strong opioids currently used for management of moderate to severe pain. From the above, it is then possible to recommend treatment with hydromorphone in acute and chronic moderate to severe pain.

The relative risks and benefits from hydromorphone are principally those of the pharmacological effects of strong opioids in general. Therefore, the efficacy of analgesic effects comes along with the emetogenic effects, constipation, and sedation and, at high doses relative to the analgesic doses required for individual patients, the potential for respiratory depression.

8. References

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